PATHOLOGY COMPETENCIES FOR MEDICAL EDUCATION AND EDUCATIONAL CASES

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Pathology Competencies for Medical Education and Educational Cases

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Current medical school curricula predominantly facilitate early integration of basic science principles into clinical practice to strengthen diagnostic skills and the ability to make treatment decisions. In addition, they promote life-long learning and understanding of the principles of medical practice. The Pathology Competencies for Medical Education (PCME) were developed in response to a call to action by pathology course directors nationwide to teach medical students pathology principles necessary for the practice of medicine. The PCME are divided into three competencies: 1) Disease Mechanisms and Processes, 2) Organ System Pathology, and 3) Diagnostic Medicine and Therapeutic Pathology. Each of these competencies is broad and contains multiple learning goals with more specific learning objectives. The original competencies were designed to be a living document, meaning that they will be revised and updated periodically, and have undergone their first revision with this publication. The development of teaching cases, which have a classic case-based design, for the learning objectives is the next step in providing educational content that is peer-reviewed and readily accessible for pathology course directors, medical educators, and medical students. Application of the PCME and cases promotes a minimum standard of exposure of the undifferentiated medical student to pathophysiologic principles. The publication of the PCME and the educational cases will create a current educational resource and repository published through *Academic Pathology*.

Keywords
pathology competencies, pathology objectives, educational cases, disease mechanisms, organ system pathology, diagnostic medicine, therapeutic pathology

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Background

Becoming a competent physician requires the ability to gain a broad foundation of knowledge, skills, and attitudes essential for independent medical practice. Essential in this is the understanding of the normal and pathological processes of each organ system, the ability to apply disease mechanisms to describe the pathobiology, and the ability to continually improve the diagnostic acumen and optimal treatment decisions through life-long learning. The initial project to develop pathology competencies was described in the article "National Standards in Pathology Education,"[1] where over 60 pathology course directors and department chairs submitted pathology course objectives that were extensively revised and peer-reviewed,

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then posted on the Association of Pathology Chairs (APC) Website in 2014, where they were available for both course directors and medical students. A website externally linked from the APC Website was maintained where anyone could leave a comment regarding the competencies. This project, the pathology competencies for medical education (PCME), was initiated and supported by the Undergraduate Medical Education Committee of the APC.[2]

Most medical schools have transitioned to an integrated organ–based curriculum,[1] where individual courses are no longer taught as distinct disciplines. The manner in which medical students are taught has also changed. The lecture format has largely been replaced with multiple types of active learning, including integrated small group discussions, team-based learning exercises, and flipped classrooms. Pathology course directors have a new challenge in education that has vastly transformed from the classic 1910 Abraham Flexner module of basic science education with individual basic science and clinical skills courses followed by 2 years of clinical practice apprenticeships[3] to an integrated and interdisciplinary medical school curriculum. In this transformation, individual disciplines are no longer presented as stand-alone courses, and the exponential expanse of medical knowledge requires an ever-changing and comprehensive understanding of pathobiology by the competent practicing physician. The importance of understanding pathobiology is underscored by the significant amount of questions included on the current US Medical Licensing Examination (USMLE), where pathobiology is tested in both Steps 1 and 3 of the licensing examinations.[4] Every medical student must master disease processes and therapeutics in order to become a competent intern, resident, and fully practicing physician. As stated in the current standard 7 of the Liaison Committee on Medical Education (LCME) publication "structures and functions of a medical school,"[5] there are important elements that must be understood including: (1) recognize and interpret symptoms and signs of disease and (2) develop differential diagnoses and treatment plans.

Pathology has a central role to assist students and physicians in (1) understanding the mechanisms of disease that lead to the signs and symptoms that must be recognized in patients, (2) forming a differential diagnosis, and (3) applying laboratory medicine that allows physicians to rule in or out individual diagnoses and make appropriate diagnostic and treatment decisions. This is in line with the Carnegie Foundation's report calling for a new reform of learning that is "learner centered"[6] and for learning outcomes to be tied to competencies.

The goal of this endeavor is 3-fold: (1) to revise the previously Website-published pathology competencies as these must be a living document, meaning revised regularly to keep pace with current medical practice and understanding, to highlight the essential (or minimum) for all medical students to understand for the practice of medicine and remain current with medical practice; (2) to emphasize laboratory medicine, which is often not taught, or at best only superficially taught, in many medical school curricula; and (3) to develop a shared resource of pathology competencies and educational cases highlighting the competencies for pathology faculty, educators, and students, which are developed by or with pathologists, peer-reviewed, and represent foundational understanding of pathobiology essential for clinical practiec that can easily be adapted into any curriculum.

Pathology Competencies for Medical Education

The PCME have detailed learning objectives under each goal that direct medical students and course directors to important facets of each learning goal that can be individually applied by learners. The competencies are divided into 3 sections—disease mechanisms and processes, organ system pathology, and diagnostic medicine and therapeutic pathology—and allow flexibility for each learning institution and learner to apply the learning goals and objectives in a way that can keep the unique design of each curriculum or learning plan. The competencies are purposefully kept broad as they represent the minimum requirements of what pathology course directors across the nation have agreed upon to prepare medical students for entry into any residency program and for the subsequent contemporary practice of medicine.[1]

The learning objectives of the competencies are meant to be a living document, being continually commented upon by pathologists, medical educators, and medical students, and revised accordingly after review by an editorial group. The topics, goals, and learning objectives, as well as the comments submitted on the PCME website before November 2016, have been extensively reviewed by the original editorial group to ensure the learning objectives are current with the changing and expanding medical knowledge. Compared with the original competencies, additional sections have been developed, learning objectives have been revised, the format has been standardized, and new introductions for each section have been added. The revised competencies are found in the following pages of this article.

Educational Cases

Following publication of the original PCME, the Undergraduate Medical Educators Section (UMEDS) of APC began developing educational cases for the pathology competencies that are current, peer-reviewed, and highlight the pathology competencies in learning cases that can easily be adapted to multiple types of educational modalities. Some of the original cases were posted on the PCME website.

The format of the cases has evolved from the original cases posted on the PCME website to the present format of educational cases that are presented in this special edition of *Academic Pathology*. The educational cases reference the PCME from the following pages, and address at least 1 primary learning objective, but may have 1 or more secondary learning objective(s). The pathology competencies and learning objectives are clearly indicated in the beginning of each case so that the focus of the educational case is evident. Key elements of the current format

include clinical presentation, discussion questions or points, learning points, and references. The clinical presentation may include images or laboratory data for the patient's presentation. The discussion questions or points are questions or statements that promote clinical reasoning followed by detailed explanations of the pathology, medicine, or therapeutics brought up in the discussion point or question. The learning points at the end of the case highlight the main teaching points from the preceding discussion. Thus, the cases demonstrate the application of medical reasoning to clinical scenarios that allow the learner to understand and apply diagnostic principles, incorporating morphologic findings and laboratory values with discussion of the laboratory medicine essentials for accurate diagnosis and treatment. References are included in each case and will allow the reader to review the original sources used to create the learning case or gain additional in-depth information. Thus, the educational cases are written in a style that can be easily used or adapted to multiple educational formats, such as small group discussions or flipped classrooms.

Discussion

Development of the PCME and the educational cases that support the individual learning objectives is a tremendous undertaking. On the broadest level, this effort supports the LCME standard 7, which requires all medical school curricula to prepare the undifferentiated medical student with sufficient breadth and depth of knowledge for the contemporary practice of medicine. This very broad view is the level at which the objectives were originally created, intended to be the minimum-level objectives course directors nationally felt were needed for adequate understanding for the practice of medicine. In addition, the PCME can be used by individual medical schools to gain leverage for additional curriculum development, especially in laboratory medicine, which is often only minimally taught, and to help expose students to pathology as a clinical specialty. Having a national repository of competencies that is peer-reviewed allows use of learning objectives and educational cases in individual curricula, potentially relieving some of the load on pathology course directors to continually update curricula to keep up with the exponential expanse of knowledge, laboratory testing, and treatment options. And lastly, a national repository of learning objectives and cases can potentially be used to support pathology exposure in integrated curricula to ensure exposure to a minimum amount of pathology for all students. We invite our audience to comment on the depth and breadth of the competencies found on the following pages.

The primary audience for the educational cases is our pathology educators, especially since not all pathology course directors are pathologists. The cases are peer-reviewed, appropriately referenced, and can be used as teaching material by faculty and students. Discussions that follow each discussion point should be broad enough to give faculty who may use these educational cases a deeper understanding of the pathobiology behind the learning objectives needed to teach or explain the concepts to the students. Here we emphasize that the discussions should explain the basic science and medicine behind each objective at a deeper level than the bare minimum of the objectives. As educators, we must be able to explain and build on basic knowledge concepts for our students, tying the information together in a tightly woven fabric across disciplines. In addition, the discussions should explain the clinical reasoning behind each of the discussion points. Thus the educational cases are not intended to be a bare-bones review, but rather a fuller discussion building on concepts and explaining the thought process that will allow our students to become critical thinkers and apply new knowledge in the future. Having said this, the cases may be adapted to different levels or types of learners during different parts of the curriculum. For example, a case may present a simple benign lesion at a basic level where the intent is to highlight histologic features that help to differentiate between benign and malignant processes, however, another case may cover that same lesion in a different scenario to highlight clinical or diagnostic aspects of that specific disease.

Examples of educational cases can be found in the following pages for a variety of objectives from the three pathology competencies. The educational cases allow for individual use of the cases as students for primary learning or inclusion in medical school curricula in an adaptable format for a variety of teaching venues including laboratories, small group discussions or Team-Based-Learning. The educational cases are intended to facilitate knowledge integration and retention essential for clinical practice. Moving forward, we invite the broader community to submit educational cases to *Academic Pathology* to grow this national resource.

Conclusion

The educational cases highlight principles of the 3 competencies—(1) disease mechanisms and processes, (2) organ system pathology, and (3) diagnostic medicine and therapeutic pathology—and are presented in a way to help the development of clinical reasoning and the application of basic science into medicine, as well as increase the diagnostic acumen and treatment of disease. Continuing to build and review the PCME and create educational cases to highlight what we as a pathology education community feel is essential knowledge for the practice of medicine requires broader input.

We encourage readers to comment on the pathology competencies to further shape what we as pathologists feel is essential for medical education. Comments regarding the PCME can be sent to Jen Norman, in the APC office, at jnorman@apcprods.org. As stated above, the competencies are a living document requiring periodic updates. Comments will be reviewed and revised competencies will be published. In addition, we invite readers to submit educational cases directly to *Academic Pathology*, following the submission guidelines found on the *Academic Pathology* website.

We are grateful to *Academic Pathology* that the PCME and educational cases will be published as an easily accessible resource for educators and students.

Pathology Competencies for Medical Education

Competency 1

Disease Mechanisms and Processes

A foundational knowledge of mechanisms of disease including the etiology, local or systemic responses to disease, consequences of disease, and cellular events involved in disease or adaptive changes is essential for understanding disease processes in organ system pathology and in patients.

There are 10 topics within this competency area. Each topic includes general learning goals and specific objectives that students should be able to meet before step 1 of the USMLE. Table 1 lists the topic areas and reference codes and shows the number of goals and objectives for each.

Table 1. Disease Mechanisms and Processes.

Topic	Number of Goals	Number of Objectives	Reference Code
Genetic mechanisms	1	6	GM
Neoplasia	3	13	N
Environmental mechanisms	2	9	EM
Metabolic and nutritional mechanisms	1	5	MN
Inflammatory mechanisms	1	8	FLAM
Immunological mechanisms	1	10	IM
Infectious mechanisms	2	16	FECT
Tissue renewal, regeneration, and repair	1	7	RRR
Hemodynamic disorders and thromboembolic disease	2	6	HDTD
Adaptation and cell death	3	7	ACD

Topic: Genetic Mechanisms (GM)

This topic includes a basic knowledge of genetic mechanisms of disease including inherited and somatic disorders with the resulting consequences leading to disorders of development, metabolism, aging, stem cell biology, immunology, and the development of cancer.

Learning Goal 1: Genetic Mechanisms of Developmental and Functional Abnormalities

Apply knowledge of the genetic mechanisms of disease to discuss how changes in the genome can cause developmental and functional abnormalities at the cellular, tissue, and organism levels.

Objective GM1.1: Types of Mutations. Describe different types of mutations that can occur in human disease, and discuss how each of these can produce abnormalities in DNA transcription and/or alterations in the type or amount of protein produced.

Objective GM1.2: Inheritance Patterns. Compare and contrast the inheritance patterns of different types of Mendelian disorders and give examples of each type of pattern.

Objective GM1.3: Genetic Diseases of Enzyme Function. Provide examples of genetic diseases associated with abnormal enzyme function, and compare and contrast with genetic diseases that produce abnormal structural proteins or other nonenzyme proteins.

Objective GM1.4: Chromosomal Abnormalities. Discuss mechanisms that result in developmental abnormalities involving abnormal chromosomal number and provide examples of diseases associated with trisomies or chromosomal deletions.

Objective GM1.5: Multifactorial Inheritance and Environmental Factors. Discuss and give examples of disorders associated with multifactorial inheritance and describe how environmental factors can interact with genetic factors to produce or modulate disease.

Objective GM1.6: Nonclassical Inheritance. Describe the pathophysiologic mechanisms that result in disorders of a nonclassical inheritance and mitochondrial inheritance and give clinical examples of each.

Topic: Neoplasia (N)

This topic includes a basic understanding of characteristics of benign and malignant neoplasms, epidemiologic and environmental factors that influence neoplastic change, as well as an understanding of the molecular basis of neoplasia including oncogenes, tumor suppressor genes, carcinogenic agents, and host defense.

Learning Goal 1: Genetic Basis of Neoplasia

Apply knowledge of the genetic basis of neoplasia to explain how genetic changes are acquired, how functional alterations in these mutated genes lead to the development of cancer, and how these alterations can be exploited with therapy.

Objective N1.1: Genetic Mechanisms of Neoplasia. Discuss and provide examples of molecular genetic mechanisms that underlie cancers, including germline mutations (including point mutations, deletions, amplifications, and translocations) and epigenetic changes.

Objective N1.2: Oncogenes and Tumor Suppressor Genes. Explain the action of oncogenes and tumor suppressor genes in growth factor–initiated signal transduction in both normal and

neoplastic cells and discuss how this information can be utilized for treatment.

Objective N1.3: Genes that Promote Growth or Inhibit Cell Death. Compare and contrast the actions of genes that promote cell growth in cancers with those that inhibit cell death and explain how this information influences the choice of therapeutic agents.

Objective N1.4: DNA Fidelity. Describe how cells maintain DNA fidelity and discuss, with examples, how mutations in these pathways produce genomic instability and clonal evolution.

Learning Goal 2: Environmental Influences on Neoplasia

Apply knowledge of the environmental factors that influence neoplastic transformation.

Objective N2.1: Prevalence and Geographic Impact on Neoplasia. Describe the prevalence of neoplastic diseases and discuss the environmental factors that influence patients as they move between geographical regions.

Objective N2.2: Mechanisms of DNA Damage Repair. Describe the mechanisms by which exposure to radiation, tobacco, alcohol, or other environmental chemical agents can produce cancer.

Objective N2.3: Influence of Viruses or Microbial Agents on Neoplasia. Describe the mechanisms by which viruses and other microbiological agents can contribute to the development of cancer.

Objective N2.4: Environmental Factors that Influence Neoplasia. Describe environmental factors that influence the incidence of common tumors.

Learning Goal 3: Characteristics of Neoplasia

Apply knowledge of the characteristics of neoplasia to discuss the morphologic appearance, classification, biological behavior, and staging of neoplasms.

Objective N3.1: Morphologic Features of Neoplasia. Describe the essential morphologic features of neoplasms and indicate how these can be used to diagnose, classify, and predict biological behavior of cancers.

Objective N3.2: Cellular Capabilities of Neoplasia. Discuss the cellular capabilities of neoplasms that enable them to invade tissues and to metastasize and recognize how this differentiates benign from malignant neoplasms.

Objective N3.3: Stromal Elements in Cancer. Discuss the dependence of cancers on stromal elements and ability to generate their own blood supply to maintain growth and explain how this information can be used to treat cancers.

Objective N3.4: Paraneoplastic Syndromes. Define and provide examples of paraneoplastic syndromes and describe how substances produced by cancers can produce systemic effects in the host.

Objective N3.5: Grading and Staging of Neoplasia. Compare and contrast the basic grading and staging of neoplastic diseases and describe the tumor, (lymph) nodes, metastasis (TNM) classification for common tumors such as breast and colon carcinoma.

Topic: Environmental Mechanisms (EM)

Etiologies including physical damage resulting from trauma, particles, extreme temperature, and radiation and chemical exposures to small molecules and biologic toxins. The mechanism of injury usually causes direct damage that initiates a host response that can lead to a range of results from the process of resolution to a chronic complicated pathologic state.

Learning Goal 1: Cell Injury

Apply knowledge of biochemistry and cellular physiology to describe the mechanisms leading to cell injury induced by exposure to external agents including radiation, environmental toxins, drugs of abuse, and therapeutic agents.

Objective EM1.1: Mechanisms of Cell Injury. Compare and contrast different mechanisms of chemical injury, specifically agents that act by direct binding to and inactivation of cellular constituents with those that require metabolic activation to induce toxicity and discuss how genetic factors affect toxicity of different agents.

Objective EM1.2: Tobacco Use. Discuss the pathogenesis of tobacco use and the resultant pathologic changes in affected organs.

Objective EM1.3: Alcohol Use. Discuss the pathogenesis of alcohol abuse and the resultant pathologic changes in affected organs.

Objective EM1.4: Drugs of Abuse. Describe the mechanism by which drugs of abuse induce central nervous system effects and discuss, with examples, toxicities associated with both chronic use and acute overdose of these drugs, and withdrawal effects.

Objective EM1.5: Occupational Exposure. Provide examples of industrial, occupational, or environmental exposures that produce disease, the resultant pathologic changes in these affected organs from chronic exposure, and indicate what organ systems are most commonly affected by which agents.

Objective EM1.6: Toxicity of Therapeutic Drugs. Discuss, with examples, how therapeutic drugs can produce toxic effects on different tissues, distinguishing between idiosyncratic and dose-dependent effects.

Objective EM1.7: Radiation. Discuss the mechanisms by which radiation damages cells and tissues and compare and contrast how ultraviolet radiation, therapeutic radiation, and acute radiation sickness produce different disease manifestations in different organ systems. Discuss which organs are susceptible and why.

Learning Goal 2: Physical Injury

Apply knowledge of biochemistry, anatomy, physiology, and mechanisms of cell injury to describe the pathogenic mechanisms of physical injury.

Objective EM2.1: Mechanical Force Injury. Compare and contrast the types of injuries associated with mechanical force (blunt vs. penetrating) with respect to effects on skin, blood vessels, and the directly affected organs and discuss systemic response to massive trauma.

Objective EM2.2: Thermal Injury. Discuss thermal injuries, comparing and contrasting the direct and systemic effects of thermal burns, hyperthermia, and hypothermia and mechanism of injury at the cellular level.

Topic: Metabolic and Nutritional Mechanisms (MN)

This topic includes the etiologic mechanisms, host responses, and disease processes leading to impairment of absorption, transport, and utilization of nutrients and oxygen, storage disorders, and disposal of waste products.

Learning Goal 1: Nutrient Deprivation or Toxicity

Apply knowledge of biochemistry and cellular physiology to explain the pathogenic mechanisms resulting from nutrient deprivation or nutrient toxicity, and the resulting pathology at the cellular, tissue, and organism levels.

Objective MN1.1: Fat- and Water-Soluble Vitamins. Compare and contrast sources of fat-soluble and water-soluble vitamins (dietary sources) with respect to absorption, metabolism, and potential toxicity.

Objective MN1.2: Vitamin-Deficiency Disease. List vitamins and minerals whose deficiency can be associated with defined pathologic states, and explain the mechanisms by which these deficiencies produce disease.

Objective MN1.3: Obesity. Discuss the etiology and pathogenesis of obesity, comparing and contrasting genetic and environmental factors, and describe common clinical consequences.

Objective MN1.4: Malnutrition. Discuss the pathologic consequences of nutritional deficiencies other than vitamin deficiencies, with emphasis on severe protein-energy malnutrition, and discuss the pathologic states that have a significant impact on nutritional requirements.

Objective MN1.5: Diet and Systemic Disease. Discuss the effect of diet and nutritional state on systemic disease, emphasizing the role it plays in the development of atherosclerosis and cancer.

Topic: Inflammatory Mechanisms (FLAM)

This topic includes the understanding of acute and chronic inflammation, patterns of inflammation, the cellular components, mediators, and systemic effects.

Learning Goal 1: Mechanisms of Inflammation

Apply knowledge of the biochemistry and cellular physiology to describe pathogenic mechanisms of acute and chronic inflammation, and the resulting pathology at the cellular, tissue, and organism levels.

Objective FLAM1.1: Acute Inflammatory Response. Describe the time course of the vascular and cellular events responsible for the acute inflammatory response to injury, and discuss the receptors and ligands that are responsible for these events.

Objective FLAM1.2: Phagocytosis. Describe phagocytosis and the molecular mechanisms of intracellular killing.

Objective FLAM1.3: Mediators of Inflammation. Discuss the chemical mediators of inflammation, classifying the mediators with respect to origins, targets, and mechanisms of action.

Objective FLAM1.4: Systemic Changes in Inflammation. Describe systemic changes seen in inflammation, including metabolic consequences of changes in levels of serum proteins (acute phase reactants) and other inflammatory mediators.

Objective FLAM1.5: Outcomes of Inflammation. Summarize the possible pathological outcomes of inflammation and discuss factors that determine what outcomes are seen under different circumstances.

Objective FLAM1.6: Morphologic Patterns of Inflammation. Recognize and classify the major types of inflammatory lesions that can be present in histologic sections, and identify the cellular and protein constituents in these lesions.

Objective FLAM1.7: Acute, Chronic, and Granulomatous Inflammation. Compare and contrast acute, chronic, and granulomatous inflammation with respect to the major cell type(s) involved in the processes, the types of etiologic agents that produce each of these, and the mechanisms of tissue injury seen with these different types of inflammation.

Objective FLAM1.8: Extravascular Fluids Associated With Injury. Classify types of extravascular fluids associated with injury based on their cellular and protein content, know the terminology used to define these, and provide examples of pathologic conditions in which these can be found.

Topic: Immunological Mechanisms (IM)

This topic includes the understanding of normal and dysregulated innate and adaptive cellular immune responses resulting in inflammation, resolution, and disease.

Learning Goal 1: Immune Dysfunction

Apply knowledge of basic mechanisms of immunology to explain how dysfunction can produce cellular injury, acute and chronic inflammation, autoimmunity, allergic reactions, and susceptibility to infection; how these changes affect organ function and the health of the organism; and how therapeutic intervention can mitigate these effects.

Objective IM1.1: Innate and Adaptive Immunity. Compare and contrast innate and adaptive immunity with respect to the molecules and cells involved in the immune response, and the role of these systems in host defense.

Objective IM1.2: Cell Types. Compare and contrast the roles played by T cells, B cells, Natural Killer (NK) cells, macrophages, and dendritic cells in the immune response.

Objective IM1.3: Cytokines. Discuss, with examples, the production of different cytokines by different immune cells, the roles that cytokines play in effecting the immune response, and how knowledge of cytokine action can be exploited in the treatment of disease.

Objective IM1.4: Hypersensitivity. Compare and contrast the mechanisms of the 4 hypersensitivity reactions with respect to the situations in which each is triggered, mechanisms of injury, resulting pathologic effects on tissue, and the ultimate clinical consequences.

Objective IM1.5: Complement. Discuss how the complement cascade is activated, the role its activation plays in both inflammation and cellular cytotoxicity, and how abnormalities in complement function can produce disease.

Objective IM1.6: Immune Tolerance. Define immunological tolerance, and describe the role that failure of tolerance plays in the development of autoimmune diseases.

Objective IM1.7: Human Leukocyte Antigen (HLA). Discuss the structure and function of human histocompatibility antigens and describe the role of this system in both transplantation and susceptibility to certain diseases.

Objective IM1.8: Transplantation. Discuss the consequences of tissue transplantation, including mechanisms and pathophysiology of graft vs. host organ rejection, and the possible therapeutic interventions that can mitigate these effects.

Objective IM1.9: Immunodeficiencies. Compare and contrast the genetic basis and inheritance patterns of the well-defined primary immunodeficiency syndromes, discuss the pathogenesis and clinical sequelae of these disorders, and describe therapeutic interventions that can mitigate or correct them.

Objective IM1.10: Secondary Immune Deficiencies. Describe the etiology, mechanisms of action, and possible clinical consequences of secondary immune deficiencies.

Topic: Infectious Mechanisms (FECT)

This topic includes the mechanisms by which microorganisms, viruses, and parasites cause disease including virulence factors produced by microorganisms and host response.

Learning Goal 1: Mechanisms of Infection

Apply knowledge of biochemical and cellular physiology to describe the pathogenic mechanisms of infectious diseases including both pathogen and host factors, the resulting pathology at the cellular, tissue, and organism levels, and clinical manifestations.

Objective FECT1.1: Host Barrier. Explain the human host barrier to infection and describe how organisms spread within the body once the barrier is broken.

Objective FECT1.2: Categories of Infective Agents. Describe the general categories of infective agents including bacteria, viruses, fungi, and parasites and describe the morphologic patterns of infectious diseases and the general mechanisms by which each of these cause disease.

Objective FECT1.3: Host Responses to Infection. Compare and contrast host responses to different classes of infectious agents in terms of morphological features, mechanisms of action, and mechanisms of immune evasion.

Learning Goal 2: Pathogenic Mechanism of Infection

Apply knowledge of biochemical and cellular physiology to describe pathogenic mechanisms; the resulting pathology at the cellular, tissue, and organism levels; and the clinical manifestations of viral, bacterial, fungal, and parasitic infections.

Objective FECT2.1: Viral Mechanisms. Compare and contrast the mechanisms by which RNA, DNA, and retroviral viruses enter and damage cells.

Objective FECT2.2: Patterns of Viral Infection. Compare and contrast viruses that result in acute transient, chronic latent, chronic productive and transformative infections and discuss how these differences result in different disease pathogenesis.

Objective FECT2.3: Histopathologic Features of Viral Infection. Compare and contrast the histopathological features of herpes virus, cytomegalovirus, human papilloma virus, and adenovirus in terms of nuclear features, inclusions, size of cells, and other unique characteristics; recognize these histopathological features of viral infections in images of different tissues.

Objective FECT2.4: Mechanisms of Bacterial Damage. Describe the mechanisms by which bacteria damage cells and tissues, comparing and contrasting mechanisms characteristic of infection with particular categories of bacteria.

Objective FECT2.5: Transmission Patterns of Bacterial Infection. Discuss the different patterns of transmission of bacterial

diseases as a function of both the type of organism and the organ systems involved in the infection.

Objective FECT2.6: Tissue Response to Bacterial Infection. Describe the histologic patterns of tissue response to bacterial infection as a function of differences in the organisms involved, the specific organ affected, and the manner by which the bacterium enters the organ.

Objective FECT2.7: Special Stains for Bacteria. Recognize and compare morphology and cell wall features of bacteria using Gram stain, Warthin Starry (silver) stain, Acid Fast stain, Partial Acid Fast stain, and Periodic Acid Schiff stain, and correlate with diagnosis.

Objective FECT2.8: Fungal Infection. List the different types of fungal organisms that infect humans and compare and contrast the mechanisms by which they damage tissues, the inflammatory responses they induce, and the resultant diseases that arise.

Objective FECT2.9: Histopathologic Features of Fungal Infection. Recognize histopathologic evidence of fungal infections and compare and contrast the histopathological features and staining characteristics of the following fungi: *Candida albicans*, *Cryptococcus neoformans*, *Aspergillus*, *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitis*, *Pneumocystis jiroveci*, and *Zygomycetes*.

Objective FECT2.10: Fungal Infection in Immunosuppression. Compare and contrast the types of fungal infections that occur in immunosuppressed and immunocompetent patients with respect to the organisms involved, the mechanisms of organ damage, and the resultant clinical manifestations.

Objective FECT2.11: Parasitic Infections. Describe classes of parasites that produce human disease, give examples of each class, and discuss their life cycle within humans and within other hosts.

Objective FECT2.12: Tissue Response to Parasitic Infection. Discuss the mechanisms of pathologic damage caused by different parasites in different tissues, and describe the diseases, complications, and possible outcomes associated with such infections.

Objective FECT2.13: Histopathologic Features of Parasitic Infection. Recognize tissues involved with parasitic infections and compare the histopathological features and staining characteristics of parasites producing the following parasitic diseases: toxoplasmosis, giardiasis, amebiasis, malaria, babesiosis, leishmaniasis, trypanosomiasis, strongyloidiasis, schistosomiasis, filariasis, and cestode infections.

Topic: Tissue Renewal, Regeneration, and Repair (RRR)

This topic includes an understanding of the pathogenesis of cellular proliferation for regeneration of cells, including of stem cells, and tissue and signal mechanisms for the repair process.

Learning Goal 1: Mechanisms of Tissue Regeneration, Renewal, and Repair

Apply knowledge of biochemistry and cellular physiology to describe the pathogenic mechanisms of tissue regeneration, renewal, and repair, the resulting pathology at the cellular, tissue, and organism levels, and describe clinical manifestations.

Objective RRR1.1: Stem Cells. Compare and contrast embryonic and adult (somatic) stem cells with respect to their ability to proliferate and differentiate into different cell types; define induced pluripotent stem cells and compare and contrast them with the other types of stem cells.

Objective RRR1.2: Cell Cycles. Describe the 5 stages of the cell cycle, and explain the role of cyclins, cyclin-dependent kinase, and other proteins in the regulation of progression through the cell cycle, and how disruption of the cell cycle can lead to disease with resultant pathology.

Objective RRR1.3: Signaling Pathways. Discuss the signaling pathways involved in the regulation of cell growth, listing important cell surface receptors, and describing the mechanisms whereby engagement of receptors by growth factors leads to cell growth.

Objective RRR1.4: Extracellular Matrix. List the important proteins of the extracellular matrix, describe the role of cell–matrix interactions in cell growth and differentiation, and provide examples of how structural alterations of matrix proteins produce disease.

Objective RRR1.5: Angiogenesis. Describe the regulation of angiogenesis, discussing receptors on vascular endothelium as well as the role soluble and stromal factors play in the process, and describe the effect of aberrant angiogenesis in certain diseases.

Objective RRR1.6: Wound Healing. Describe the phases of cutaneous wound healing, the mechanisms of healing by first intention (primary union) and second intention (secondary union) and possible clinical consequences of abnormal wound healing.

Objective RRR1.7: Anti-inflammatory Drugs and Wound Repair. Explain the effects of anti-inflammatory medications on wound repair.

Topic: Hemodynamic Disorders and Thromboembolic Disease (HDTD)

This topic includes a basic knowledge of edema, congestion, and shock as well as a basic understanding of the coagulation cascade to understand the pathogenesis of thromboembolic disorders.

Learning Goal 1: Hemodynamics and Shock

Apply knowledge of the biochemical and cellular physiology to discuss the pathogenic mechanisms resulting in alterations in hemodynamics and shock. Describe the resulting pathology at the cellular, tissue, and organism level and describe clinical manifestations associated with these pathologic changes.

Objective HDTD1.1: Edema. Describe the pathophysiologic categories of edema and compare and contrast, with examples, how edema can be produced as a result of changes in hydrostatic pressure or plasma oncotic pressure.

Objective HDTD1.2: Hyperemia and Hemorrhage. Explain the clinical, morphological, and physiological significance of hyperemia, congestion, and hemorrhage, with respect to the disease states that cause them.

Objective HDTD1.3: Shock. Classify different types of shock according to etiology and compare and contrast the pathogenesis of these different types.

Learning Goal 2: Clotting and Disruption of Blood Flow

Apply knowledge of the biochemical and cellular physiology to discuss pathogenetic mechanisms that result in alterations in blood clotting or other disruptions to blood flow. Describe the resulting pathology at the cellular, tissue, and organism level and the clinical manifestations associated with these pathologic changes.

Objective HDTD2.1: Blood Clotting. Discuss the vascular, cellular, and humoral events involved in blood clotting and provide examples of genetic or acquired factors that can lead to either excess clotting or bleeding.

Objective HDTD2.2: Thrombosis and Thromboembolism. Compare and contrast thrombosis in situ and thromboembolism with respect to sites of involvement, risk factors, and attendant pathologic and clinical consequences.

Objective HDTD2.3: Embolism. Compare and contrast the etiology and clinical consequences of different types of embolism.

Topic: Adaptation and Cell Death (ACD)

This topic includes a basic understanding of the cellular responses to cellular stress, mechanisms of cellular injury, and differentiating necrosis and apoptosis.

Learning Goal 1: Cellular Response to Injury

Apply knowledge of membrane physiology, metabolism, signal transduction, and macromolecular synthesis to discuss cellular responses to injury at the cell, tissue, and organism levels; how these responses affect morphologic appearance; and how they can be used for diagnostic, prognostic, and therapeutic purposes.

Objective ACD1.1: Adaptation. Discuss the pathogenesis of hyperplasia, hypertrophy, atrophy, and metaplasia, and compare and contrast their possible physiologic and pathologic causes.

Objective ACD1.2: Necrosis. Define necrosis and compare and contrast the forms of necrosis produced in response to different etiologic agents with respect to their variable clinical and morphologic features.

Objective ACD1.3: Ischemia. Compare and contrast ischemia and hypoxia and discuss the time course of the molecular events that occur in a cell in response to lack of oxygen, emphasizing the events that distinguish reversible from irreversible injury.

Objective ACD1.4: Reperfusion Injury. Summarize the cell's response to reperfusion injury emphasizing how reperfusion can exacerbate injury produced by ischemia.

Learning Goal 2: Cell Death

Apply knowledge of biochemistry and cellular physiology to differentiate between pathogenic and physiologic mechanisms of cell death, the resulting morphologic appearance, and the physiologic and clinical settings in which these mechanisms are activated.

Objective ACD2.1: Apoptosis. Contrast the etiology, mechanisms, and morphologic changes of apoptosis with those of necrosis. Discuss the circumstances in which dysregulation of apoptosis can produce disease, and circumstances that determine why cells undergo apoptosis vs. necrosis.

Learning Goal 3: Sublethal Injury

Apply knowledge of cellular physiology, metabolism, and macromolecular synthesis to discuss cellular and subcellular responses to sublethal injury or stress on cells; how these responses affect morphologic appearance at the cell and tissue level; and how they can affect organ function.

Objective ACD3.1: Cellular Response to Environmental Changes. Discuss, with examples, the changes that occur in cellular organelles or cytoskeletal proteins of different cell types in response to environmental alterations.

Objective ACD3.2: Intracellular Accumulations. Describe the mechanisms of intracellular accumulations and the morphologic and clinical consequences of these accumulations.

Competency 2

Organ System Pathology

Once the student has mastered the fundamental mechanisms and processes for causing, sustaining, extending, or resolving injury, this knowledge can be integrated to understand how pathology in each organ system affects the initial pathologic site, multi-organ systems, and the overall function of the patient.

There are 23 topics within this competency area. Each topic includes general learning goals and specific objectives that medical students should be able to meet upon graduation from medical school. Table 2 lists the topic areas and shows the number of goals and objectives for each.

Table 2. Organ System Pathology.

Topic	Number of Goals	Number of Objectives	Reference Code
Cardiovascular: blood vessels	3	10	CBV
Cardiovascular: heart	6	22	CH
Hematopathology: red cell disorders	1	7	HRC
Hematopathology: white cell disorders	7	28	HWC
Hematopathology: platelets and coagulation disorders	2	19	HPCD
Respiratory system	4	26	RS
Head and neck	2	7	HN
Gastrointestinal tract	8	22	GT
Hepatobiliary	7	23	HB
Pancreas	2	5	P
Kidney	5	17	UTK
Bladder	3	10	UTB
Male reproductive: prostate	2	6	MP
Male reproductive: testes	2	5	MT
Breast	2	11	BR
Female reproductive: uterus, cervix, and vagina	4	10	FU
Female reproductive: ovary	2	6	FO
Female reproductive: disorders of pregnancy	1	7	FDP
Endocrine	6	19	EN
Skin	5	11	SK
Musculoskeletal system	2	12	MS
Nervous system: CNS	7	27	NSC
Nervous system: PNS and eye	3	7	NSP

Abbreviations: CNS, central nervous system; PNS, peripheral nervous system.

Topic: Cardiovascular—Blood Vessels (CBV)

Cardiovascular disorders resulting from abnormal development, hypoxia, immune dysregulation, infections and smooth muscle changes as they relate to the blood vessels are enumerated.

Learning Goal 1: Mechanisms of Atherosclerosis

Apply knowedge of immunologic principles, inflammation, and tissue repair to explain atherosclerosis and its complications.

Objective CBV1.1: Factors Contributing to Endothelial Injury. Explain how environmental factors (including elevated cholesterol and LDL complexes, infection, and smoking) can contribute to endothelial cell injury.

Objective CBV1.2: Feedback in Endothelial Damage. Describe the positive feedback loop in which damaged endothelial cells cause further endothelial damage.

Objective CBV1.3: Atherosclerosis Plaque Rupture. Predict the local and distant consequences that are likely to follow rupture of an atherosclerotic plaque and the resultant clinical presentation.

Objective CBV1.4: Vascular Aneurysm. Describe the morphologic changes in atherosclerosis and discuss how atrophic changes in the vessel wall may result in aneurysm formation.

Learning Goal 2: Vascular Damage and Thrombosis

Apply knowledge of the cellular response to injury and basic hemodynamic principles to explain how defective or excessive inflammatory and reparative processes damage blood vessels and how this damage results in thrombus formation.

Objective CBV2.1: Thrombus Formation. Discuss the steps in thrombus formation and its predisposing factors.

Objective CBV2.2: Aortic Aneurysm and Dissection. Compare and contrast aortic aneurysms and aortic dissections in terms of their predisposing factors, the sites of involvement, and patient populations likely to be affected.

Objective CBV2.3: Abdominal Aortic Aneurysm. Describe the clinical consequences of an abdominal aortic aneurysm.

Learning Goal 3: Vasculitis

Apply knowledge of microbiological principles and mechanisms of immunologically mediated disease to discuss the pathogenesis, clinical presentation, morphological features, and laboratory diagnosis of the different vasculitides.

Objective CBV3.1: Drug-induced Vasculitis. Describe how a drug-induced vasculitis depends on a functioning immune system.

Objective CBV3.2: Autoimmune Vasculitis. Compare and contrast the mechanisms by which an autoimmune disease can appear as a vasculitis in 1 specific organ or as a generalized disease in many organs.

Objective CBV3.3: Categories of Vasculitis (Vessel Size). Describe the vasculitides that occur in large, medium, and small vessels.

Topic: Cardiovascular—Heart (CH)

Cardiovascular disorders resulting from abnormal development, hypoxia, immune dysregulation, infections and intrinsic muscle disease as they relate to the heart are enumerated.

Learning Goal 1: Heart Failure

Apply knowledge of anatomy, physiology, and general pathophysiologic principles to describe the clinical presentation associated with heart failure.

Objective CH1.1: Right- and Left-Sided Heart Failure. Compare and contrast right heart versus left heart failure in terms of clinical features, pathologic features, and the short-term and long-term consequences.

Objective CH1.2: Cardiomyopathy. Compare and contrast the clinicopathologic features of dilated, restrictive, and hypertrophic cardiomyopathies.

Learning Goal 2: Atherosclerosis in Heart Disease

Apply knowledge of anatomy, physiology, and general pathophysiologic principles to explain how atherosclerosis leads to heart disease and death.

Objective CH2.1: Ischemic Heart Disease. Explain how ischemic heart disease can progress while remaining entirely free of symptoms for many years.

Objective CH2.2: Angina. Contrast the clinical, physiologic, and histologic differences between exercise-induced angina and unstable angina.

Objective CH2.3: Reperfusion Versus Ischemic Injury. Contrast the behavior of the myocardium that has been subjected to chronic ischemia alone from that of reperfused myocardium following therapy for infarction.

Objective CH2.4: Timing of Changes in Myocardial Infarction. Compare and contrast the gross and microscopic features of acute myocardial infarction and remote myocardial infarction, and at what point gross or microscopic pathology appears.

Objective CH2.5: Histopathology of Myocardial Infarction. Describe the histologic features of acute myocardial infarction and explain the pathophysiology underlying the histologic changes from initial infarction through fibrosis and relate to the laboratory diagnosis of myocardial infarction.

Objective CH2.6: Complications of Myocardial Infarction. Identify short-term and long-term complications of myocardial infarction.

Learning Goal 3: Cardiovascular Malformation

Apply knowledge of embryologic principles to describe how improper development of the heart and blood vessels leads to cardiac dysfunction.

Objective CH3.1: Congenital Heart Disease. Name the most common forms of congenital heart disease and outline their clinical presentation, natural history, and long- and short-term complications.

Objective CH3.2: Congenital Heart Disease Associated with Genetic Disorders. Name several common genetic disorders associated with congenital heart disease, and describe the clinical presentation.

Objective CH3.3: Paradoxical Embolism. Describe a paradoxical embolus in terms of congenital heart disease.

Objective CH3.4: Cardiac Shunts. Define the concepts of left to right shunt, right to left shunt, and shunt reversal, and correlate with clinical presentation.

Learning Goal 4: Cardiac Infection

Apply knowledge of immunological and microbiological principles to explain the role of infectious agents in myocardial dysfunction and describe the related clinical presentations.

Objective CH4.1: Rheumatic Fever. Describe the major manifestations of rheumatic fever and its effect on the endocardium, myocardium, and pericardium.

Objective CH4.2: Rheumatic Fever and Endocarditis. Compare the effects of rheumatic fever and bacterial endocarditis on the endocardium, myocardium, and pericardium.

Objective CH4.3: Infective Endocarditis. Describe the 2 major patterns of infective endocarditis and the pathologic changes seen in the cardiac valves.

Objective CH4.4: Noninfective Endocarditis. Discuss the pathologic features of noninfective endocarditis on the cardiac valves.

Objective CH4.5: Myocarditis. Describe the clinicopathologic features of myocarditis.

Objective CH4.6: Pericarditis. Summarize the common causes of pericarditis and their pathophysiologic features.

Learning Goal 5: Valvular Dysfunction

Apply knowledge of the anatomy and physiology of heart valves to explain how valvular dysfunction leads to heart failure and describe the related clinical presentation.

Objective CH5.1: Valve Stenosis. Discuss the complications associated with aortic stenosis.

Objective CH5.2: Valve Insufficiency. Describe the clinicopathologic features of mitral valve prolapse.

Learning Goal 6: Hypertension and the Heart

Apply knowledge of the mechanism of response of cardiac muscle to increased resistance to describe the clinical and pathologic changes seen in systemic and pulmonary hypertension.

Objective CH6.1: Cardiac Changes in Pulmonary Hypertension. Describe the gross and microscopic adaptive changes in the myocardium that result from pulmonary hypertension.

Objective CH6.2: Cardiac Changes in Systemic Hypertension. Discuss the pathogenesis of hypertension and the gross and microscopic adaptive changes in the myocardium that result from systemic hypertension.

Topic: Hematopathology—Red Cell Disorders (HRC)

Red blood cell disorders resulting from abnormal development, nutritional derangements, inherited disorders, and intrinsic disease as they relate to anemia are enumerated.

Learning Goal 1: Anemia

Apply knowledge of nutritional biochemistry, erythropoiesis, and red blood cell structure and function to a discussion of the behavioral, hereditary, developmental, and chronic causes of anemia.

Objective HRC1.1: Iron-Deficiency Red Blood Cell Development. Explain the contribution of iron to red blood cell development and function. Describe behaviors and conditions that lead to iron deficiency and contrast the morphology and laboratory parameters of normal red cells versus iron-deficient cells.

Objective HRC1.2: Hereditary Spherocytosis. Discuss the pathophysiology of hereditary spherocytosis.

Objective HRC1.3: Hepcidin Regulation, Iron Overload, and Anemia of Chronic Disease. Discuss the role of hepcidin as an iron regulator and describe how different types of alterations in the hepcidin pathway can produce anemia of chronic disease or iron overload.

Objective HRC1.4: B12 and Folate Deficiencies. Discuss the role of vitamin B12 and folic acid in red cell development and describe the pathophysiology of anemia arising from B12 and folic acid deficiency.

Objective HRC1.5: Anemias of Red-Cell Destruction. Explain the mechanisms by which anemia is produced on the basis of shortened red cell survival, distinguishing between intrinsic and extrinsic causes of red cell destruction.

Objective HRC1.6: Aplastic Anemia. Compare and contrast congenital and acquired forms of aplastic anemia.

Objective HRC1.7: Hemoglobinopathies and Thalassemia. Describe the structural alterations and regulatory abnormalities associated with hemoglobinopathies and thalassemia, and discuss how these abnormalities give rise to the clinical manifestations of these diseases.

Topic: Hematopathology—White Cell Disorders, Lymph Nodes, Spleen, and Thymus (HWC)

White blood cell disorders resulting from abnormal development, genetic mutations, infections, and intrinsic disease as they relate to reactive and neoplastic abnormalities are enumerated.

Learning Goal 1: Development of White Blood Cells and Nonneoplastic Causes of Neutropenia

Apply knowledge of anatomy and physiology to describe the normal development of white blood cells and nonneoplastic conditions leading to increased or decreased numbers of white blood cells.

Objective HWC1.1: Morphology of White Cells. Describe the maturational pathway of white blood cells, naming and describing the morphology of the cells present at each stage for each white blood cell type.

Objective HWC1.2: White Cell Growth Factors. Define the role of growth factors in the development and maturation of white blood cells.

Objective HWC1.3: Leukocytosis. Define leukocytosis, describe several etiologies leading to it, and contrast it with leukemoid reaction.

Objective HWC1.4: Leukopenia. Compare and contrast the causes, mechanisms, and consequences of neutropenia and lymphopenia.

Objective HWC1.5: Neutrophilia. Describe the common causes for neutrophilia, lymphocytosis, monocytosis, eosinophilia, and basophilia.

Objective HWC1.6: Neutropenia. Discuss the common causes for neutropenia, lymphopenia, and leukopenia and compare with pancytopenia.

Learning Goal 2: Genetic Mutations in Hematologic Malignancy

Apply knowledge of general concepts of neoplasia to explain how genetic mutations can produce hematologic malignancies and how the clinical behavior of different malignancies can be explained by different mutations.

Objective HWC2.1: Germline and Somatic Mutations in Hematologic Malignancy. Explain the difference between germline and somatic mutations; give examples and explain how each mutation contributes to the development of hematologic malignancies.

Objective HWC2.2: Translocations in Oncogenes. Compare and contrast, with examples, translocations that result in malignancy by activation of oncogenes with those that produce fusion proteins.

Objective HWC2.3: Cell Proliferation or Cell Death in Lymphomas. Explain with examples how dysregulation of cell proliferation or of cell death can give rise to lymphomas, and compare and contrast diseases arising by each mechanism with respect to morphologic appearance and clinical behavior.

Objective HWC2.4: Molecular Basis of Leukemia and Lymphoma. Describe how understanding the molecular pathogenesis of leukemia and lymphoma can suggest targets for therapeutic intervention and give examples of diseases currently treated by targeted therapy.

Objective HWC2.5: Multiple Myeloma. Describe the clinicopathologic features of multiple myeloma in terms of clinical presentation, laboratory findings, radiologic findings, histologic features, and prognosis.

Learning Goal 3: Classification of Leukemia and Lymphomas

Apply knowledge of hematopoiesis to discuss the pathophysiologic basis for the classification of leukemia and lymphomas.

Objective HWC3.1: Morphology of Acute Leukemia and Lymphoma. Describe the morphologic features that characterize typical cases of acute leukemia and lymphoma.

Objective HWC3.2: Myeloid Neoplasia. Compare and contrast myelodysplastic syndromes, myeloproliferative neoplasms, and acute myeloid leukemia with respect to morphologic appearance, clinical features, and underlying pathophysiology.

Objective HWC3.3: Categories of Lymphoma. Compare and contrast low-grade or indolent lymphomas and high-grade or aggressive lymphomas with respect to underlying pathophysiology that yields specific morphologic features and clinical behavior.

Objective HWC3.4: Morphology of Acute Versus Chronic Leukemia. Discuss the morphologic appearance of a blast and be able to distinguish acute myeloid leukemia from chronic myelogenous leukemia.

Objective HWC3.5: Morphology of Lymphomas. Describe the histologic appearance of typical cases of follicular lymphoma, diffuse large B-cell lymphoma, small lymphocytic lymphoma/chronic lymphocytic leukemia, and Hodgkin lymphoma.

Objective HWC3.6: Hodgkin and Non-Hodgkin Lymphoma. Compare and contrast Hodgkin lymphoma with at least 2 non-Hodgkin lymphomas with respect to age and clinical symptoms at presentation, sites and pattern of spread of disease, cell of origin, histologic appearance, and prognosis and response to therapy.

Learning Goal 4: Clinical Features of Hematolymphoid Neoplasms

Discuss the clinical manifestations of hematolymphoid neoplasms including age distribution of different tumors, presenting symptoms and signs, disease complications, natural history, and response to therapy.

Objective HWC4.1: Clinical Features of Bone Marrow Neoplasms. Identify the tumors of bone marrow most likely to present with anemia, leukopenia, or thrombocytopenia and discuss the presenting clinical features most likely to be associated with each.

Objective HWC4.2: B Symptoms in Hematolymphoid Neoplasia. Define B symptoms, list which lymphomas are most and least likely to be associated with them, and discuss the prognostic implications of B symptoms in these diseases.

Objective HWC4.3: Staging of Hematolymphoid Neoplasia. Define staging as it applies to lymphoma and give examples of different lymphomas in which staging has different clinical implications.

Objective HWC4.4: Extranodal Lymphoma. Identify lymphomas most likely to present in or involve extranodal sites such as the gastrointestinal tract, bone marrow, blood, skin, or central nervous system.

Learning Goal 5: Stem Cells in Hematolymphoid Neoplasia

Describe how stem cells give rise to the diverse cell populations seen in bone marrow and lymph nodes and discuss how knowledge of hematopoietic cell development can provide a framework for understanding hematolymphoid neoplasia.

Objective HWC5.1: Cell of Origin and the Morphology of Neoplasia. Outline, with examples, the difference between the cell of origin of a neoplasm and the morphologic expression of that disease.

Objective HWC5.2: Stem Cells in Myeloid Leukemias. Discuss the evidence that supports the existence of stem cells in myeloid leukemias and list the features of chronic myeloproliferative neoplasms that suggest they are derived from stem cells.

Objective HWC5.3: Lymphoid Response to B-Cell Activation. Describe the morphologic and molecular changes that take place within a lymph node in response to B-cell activation and explain how these changes relate to different types of B-cell non-Hodgkin lymphoma.

Learning Goal 6: Thymus

Thymus Apply knowledge of the anatomy and function of the thymus to summarize how developmental anomalies, immune disorders, and malignant transformation of epithelial and lymphoid cells lead to immune dysfunction.

Objective HWC6.1: Thymoma. Compare and contrast thymoma from lymphoma and describe the clinicopathologic features of thymic neoplasms.

Objective HWC6.2: Thymic Development. Explain how deficits in particular stages of thymic development can produce specific types of disease.

Learning Goal 7: Spleen

Apply knowledge of the anatomy and function of the spleen to explain how developmental anomalies, immune, and metabolic disorders neoplasia lead to splenic dysfunction.

Objective HWC7.1: Splenic Function. Explain the contribution of normal splenic function to nonneoplastic diseases.

Objective HWC7.2: Splenomegaly. Describe the clinicopathologic features of neoplastic and nonneoplastic disorders leading to splenomegaly.

Topic: Hematopathology—Platelets and Coagulation Disorders (HPCD)

Platelet disorders resulting from abnormal development, inherited disorders, immune, and infectious diseases and their central role in blood clotting as they relate to coagulation and hemostasis abnormalities are enumerated.

Learning Goal 1: Platelets

Apply knowledge of platelet structure and function to discuss qualitative and quantitative disorders leading to abnormal bleeding.

Objective HPCD1.1: Platelets in Hemostasis. Summarize the role played by platelets in hemostasis, including platelet adhesion, activation, and aggregation.

Objective HPCD1.2: Thrombocytopenia. Identify the examples of each of the following pathogenetic categories of thrombocytopenia: decreased production, decreased platelet survival, sequestration, dilutional effect.

Objective HPCD1.3: Thrombocytopenic Syndromes. Compare and contrast the following thrombocytopenia syndromes: immune thrombocytopenic purpura, drug-induced thrombocytopenia, heparin-induced thrombocytopenia.

Objective HPCD1.4: Thrombocytopenic Purpura. Compare and contrast thrombotic thromobocytopenic purpura with hemolytic uremic syndrome.

Objective HPCD1.5: Platelet Disorders. Explain the biochemical basis of the following congenital and acquired defective platelet disorders: Bernard-Soulier syndrome, Glanzmann thrombasthenia, storage pool disorders, aspirin-related dysfunction, uremia-related dysfunction.

Objective HPCD1.6: Bone Marrow Aplasia. Explain the bases of marrow aplasia/myelophthisis, nutritional deficiency, and myelodysplasia as causes of thrombocytopenia form of marrow failure.

Learning Goal 2: Hemostasis

Apply knowledge of normal hemostasis, interaction of platelets, and procoagulant and anticoagulant factors to describe qualitative and quantitative disorders leading to abnormal bleeding and thrombosis.

Objective HPCD2.1: Types of Hemorrhage. Distinguish among the following manifestations of hemorrhage: hematoma, petechiae, purpura, and ecchymoses.

Objective HPCD2.2: Stages of Hemostasis. Compare and contrast the following stages of hemostasis: vasoconstriction, primary hemostasis, secondary hemostasis, and antithrombotic counterregulation.

Objective HPCD2.3: Secondary Hemostasis. Outline the process of secondary hemostasis, in terms of intrinsic pathway, extrinsic pathway, common pathway, fibrin formation, and fibrinolysis.

Objective HPCD2.4: Proteases and the Coagulation Cascade. Describe how particular proteins that regulate the proteases to activate the clotting cascade either promote or inhibit coagulation.

Objective HPCD2.5: Mechanisms of Hypercoagulability. Compare and contrast the roles of endothelial injury, stasis, and alterations in the regulation of blood clotting in the development of the hypercoagulable state.

Objective HPCD2.6: Risk Factors for Thrombophilia. Give examples and discuss the pathophysiology of inherited versus acquired conditions that increase the risk of thrombophilia.

Objective HPCD2.7: Disseminated Intravascular Coagulopathy. Discuss disseminated intravascular coagulopathy (DIC) in terms of etiologies, pathogenesis, clinical presentation, and course.

Objective HPCD2.8: Inherited Hemophilia. Discuss the pathogenesis and clinical and laboratory manifestations of hemophilia A and explain how it differs from hemophilia B.

Objective HPCD2.9: Vitamin K and Liver Disease. Describe the pathogenesis and clinical and laboratory findings in liver disease and vitamin K deficiency.

Objective HPCD2.10: von Willebrand Disease. Compare and contrast types I, II, and III von Willebrand disease and explain the quantitative or qualitative abnormalities and the laboratory features observed in each type.

Objective HPCD2.11: Antiphospholipid Antibody Syndrome. Describe the pathogenesis and clinical and laboratory findings in antiphospholipid antibody syndrome.

Objective HPCD2.12: Heparin-Induced Thrombocytopenia. Explain the mechanism of heparin-induced thrombocytopenia/thrombosis and describe its clinical presentation and approach to therapy.

Objective HPCD2.13: Thrombophilia in Cancer. Explain the risk of thrombophilia in cancer, describe the context of Trousseau syndrome, and give classic examples of malignancies associated with thrombophilia.

Topic: Respiratory System (RS)

Respiratory disorders resulting from abnormal development, genetic mutations, immune, infections, and intrinsic disease as they relate to lung abnormalities are enumerated.

Learning Goal 1: Vascular Diseases of the Lung

Apply knowledge of the structure and function of blood vessels to explain the pathogenesis, clinical manifestations, and pathologic findings in pulmonary embolism, pulmonary hypertension, and diffuse pulmonary hemorrhage syndromes.

Objective RS1.1: Clinical Features of Pulmonary Embolism. Compare and contrast the clinical manifestations, radiographic and

pathologic findings, and potential consequences of pulmonary embolism in terms of single versus multiple, and small versus large emboli.

Objective RS1.2: Conditions Predisposing to Pulmonary Embolism. Discuss the factors, including underlying conditions, which can impact the incidence and clinical significance of pulmonary embolism.

Objective RS1.3: Pulmonary Hypertension. Describe the structural cardiopulmonary conditions that are frequently associated with pulmonary hypertension.

Objective RS1.4: Conditions Contributing to Pulmonary Hypertension. Explain how each of the following cardiopulmonary conditions contributes to pulmonary hypertension: increased pulmonary blood flow or pressure, increased pulmonary vascular resistance, or left heart resistance to blood flow.

Objective RS1.5: Pathogenesis of Pulmonary Hypertension. Describe the pathogenesis of pulmonary hypertension in hereditary and secondary forms and the characteristic gross and microscopic morphologic features of each.

Objective RS1.6: Goodpasture Syndrome and Wegener Granulomatosis. Compare and contrast the clinical manifestations, pathogenesis, and pathologic findings in Goodpasture Syndrome and granulomatosis with polyangiitis (Wegener Granulomatosis).

Learning Goal 2: Pulmonary Infection

Apply knowledge of the local pulmonary defense mechanisms and systemic host resistance to infection to discuss pathogenesis, classification, clinical manifestations, and pathologic findings in lower respiratory tract infections in immunocompetent and immunocompromised hosts.

Objective RS2.1: Pulmonary Infections in the Immunocompromised Patient. Discuss the common infectious agents that produce pulmonary disease that are generally associated with defects in innate, humoral, or cell-mediated immunity.

Objective RS2.2: Classification of Pneumonia by Agent. Describe the classification of pneumonias by clinical setting and name the common etiologic agents for each category.

Objective RS2.3: Clinical Features of Pneumonia. Compare and contrast the clinical presentation and manifestations, gross and microscopic pathology, prognosis, and potential complications for each category of pneumonia.

Objective RS2.4: Categorization of Pneumonia. Define bronchopneumonia, lobar pneumonia, and atypical pneumonia/interstitial pneumonitis and compare and contrast the common etiologic agents and pathologic findings for each.

Objective RS2.5: Tuberculosis. Compare and contrast the clinical presentation and gross and microscopic findings in primary, secondary/reactivation, and miliary tuberculosis.

Objective RS2.6: Influenza. Define antigenic drift and antigenic shift in influenza viruses and discuss how these can result in epidemics and pandemics.

Objective RS2.7: Clinical Features of Upper- and Lower-Respiratory Infections. Compare and contrast the pathologic findings in upper and lower respiratory tract influenza infections.

Objective RS2.8: Aspiration Pneumonia. Name risk factors for aspiration pneumonia and describe the pathology, prognosis, and potential complications.

Objective RS2.9: Lung Abscess. Define lung abscess in terms of pathogenesis, typical microorganisms, clinical presentation and course, and pathologic findings.

Objective RS2.10: Fungal Pneumonia. Compare and contrast the causative agents, geographic locations, clinical presentation, and pathologic findings in chronic pneumonia caused by fungal organisms.

Objective RS2.11: Features of Pulmonary Infections in the Immunocompromised and Immunocompetent. Discuss the differences in clinical presentation and etiologic agents of pneumonia in immunocompetent versus immunocompromised hosts.

Learning Goal 3: Lung Neoplasia

Apply knowledge of the molecular basis of neoplasia to describe clinical presentation, biologic behavior, morphologic appearance, classification, diagnosis, prognosis, and targeted therapy of lung neoplasms.

Objective RS3.1: Lung Neoplasms. Describe the common locations for the different types of lung cancer.

Objective RS3.2: Morphologic Features of Lung Neoplasms. Discuss key gross and histopathologic features that may help differentiate between small cell, adenocarcinoma, and squamous cell carcinoma.

Objective RS3.3: Metastatic Carcinoma to the Lung. Describe features that favor the diagnosis of metastatic carcinoma over a primary lung tumor.

Objective RS3.4: Genetics of Lung Cancer. Describe the contribution of specific genetic mutations that are found in particular lung cancers and explain how these mutations affect therapeutic decisions.

Objective RS3.5: Environmental Factors Predisposing to Lung Cancer. Explain the environmental factors that predispose to the development of lung cancer and illustrate how these factors interact with genetic factors in the development of cancer.

Learning Goal 4: Obstructive Diseases of the Lung

Apply knowledge of the genetic and environmental factors leading to cell injury to explain the clinical and pathophysiological consequences that result in obstruction to airflow.

Objective RS4.1: Emphysema. Describe the role of smoking in emphysema; name the 4 different types of emphysema, which is most common, and which lobes of the lungs are most involved in centrilobular emphysema.

Objective RS4.2: Bronchiectasis. Explain the gross morphologic changes associated with bronchiectasis and name 2 diseases that may lead to bronchiectasis.

Objective RS4.3: Pneumoconiosis. Describe the clinicopathologic features identified with common forms of pneumoconiosis.

Objective RS4.4: Asthma. Compare and contrast the clinicopathologic features and causes of asthma and describe the morphologic changes and consequences that result in airflow obstruction.

Topic: Head and Neck (HN)

Head and neck disorders resulting from abnormal development, genetic mutations, immune, and intrinsic disease as they relate to salivary and upper respiratory abnormalities are enumerated.

Learning Goal 1: Nonneoplastic Salivary Gland Disorders

Apply knowledge of the structure and function of the salivary glands to an understanding of the clinicopathologic features associated with disorders presenting with gland enlargement.

Objective HN1.1: Salivary Duct Obstruction. Describe the potential causes for obstruction of the salivary gland duct.

Objective HN1.2: Lymphocytic Sialadenitis. Discuss disorders arising from lymphocytic infiltration of the salivary glands and discuss their potential neoplastic complications.

Objective HN1.3: Sjögren Syndrome. Describe Sjögren syndrome and discuss how it relates to salivary gland dysfunction, its effect on multiple organ systems, complications, and long term risks.

Learning Goal 2: Head and Neck Neoplasia

Apply knowledge of the etiology, pathogenesis, morphological appearance; and classification of neoplasms involving the salivary glands, oral cavity, upper airways, and larynx to their diagnosis; and prediction of biological behavior, prevention, and treatment.

Objective HN2.1: Benign and Mucoepidermoid Tumors of Salivary Glands. Distinguish the clinicopathologic features of the 2 benign tumors (pleomorphic adenoma or mixed tumor and Warthin tumor) from the malignant mucoepidermoid carcinoma.

Objective HN2.2: Squamous Cell Carcinoma of the Oropharynx. Discuss the pathogenesis of squamous cell carcinoma of the oropharynx and the spectrum of histologic findings from normal mucosa to invasive disease.

Objective HN2.3: Causes of Oropharyngeal Squamous Cell Carcinoma. Compare and contrast human papillomavirus (HPV)-driven and alcohol-/tobacco-driven development of squamous cell carcinoma including precursor lesions, tumor formation and progression, anatomic location, and survival rate.

Objective HN2.4: Developmental Neck Masses and Other Neck Tumors. Compare and contrast developmental lesions that present as masses in the neck (branchial cyst and thyroglossal duct cyst) from a paraganglioma including pathogenesis and morphologic features of each.

Topic: Gastrointestinal Tract (GT)

Gastrointestinal (GI) tract disorders resulting from abnormal development, genetic mutations, immune, infections, and intrinsic disease as they relate to the esophagus, small, and large intestine abnormalities are enumerated.

Learning Goal 1: Embryology of the Gut

Apply knowledge of the embryology of the foregut, midgut, and hindgut to summarize the morphological features and clinical presentation of developmental anomalies.

Objective GT1.1: Congenital Disorders of the Gut. Discuss the clinicopathological features of tracheoesophageal fistula, pyloric stenosis, intestinal atresia, Meckel diverticulum, and Hirschprung disease.

Learning Goal 2: Anatomy and Blood Supply of the Gut

Apply knowledge of the gross anatomy of the GI tract and hemodynamic principles to discuss vascular disorders.

Objective GT2.1: Ischemic Disorders of the Gut. Explain the pathogenesis and clinicopathological features for common disorders of the GI tract that arise from hypoxia or ischemia.

Objective GT2.2: Necrotizing Enterocolitis. Compare and contrast the pathophysiology of necrotizing enterocolitis from bowel infarction due to shock and atherosclerosis.

Learning Goal 3: Gastrointestinal Neoplasia

Apply knowledge of the molecular basis of neoplasia to explain the clinical presentation, inheritance risk, biologic behavior, morphologic appearance, classification, diagnosis, prognosis, and targeted therapy of gastrointestinal neoplasms.

Objective GT3.1: Precursors to Bowel Carcinoma. Discuss the precursor lesions, risk factors, and hereditary cancer syndromes that lead to GI neoplasia.

Objective GT3.2: Molecular Basis of Bowel Neoplasms. Summarize the molecular basis and clinicopathologic features, local and systemic, for esophageal cancer, gastric cancer, GI lymphoma, GIST, colon, and anal cancer.

Objective GT3.3: Esophageal Carcinoma. Describe the location of adenocarcinomas versus squamous cell carcinomas of the esophagus and list the major risk factors for each.

Objective GT3.4: Colon Carcinoma. Discuss the 2 most important prognostic factors for colon cancer and explain why they are most important.

Objective GT3.5: Colonic Polyps. Compare and contrast the different types of polyps and their risk of developing cancer.

Learning Goal 4: Features of Gastrointestinal Neoplasms

Apply knowledge of the gross anatomy of the GI tract and its blood supply to describe presenting signs and symptoms and pattern of spread of gastrointestinal neoplasms.

Objective GT4.1: Right- and Left-Sided Colon Carcinoma. Distinguish between carcinomas arising in the left and right colon in terms of symptoms and morphology.

Objective GT4.2: Staging of Colon Carcinoma. Describe how colon cancers are staged and list the common sites of metastases.

Learning Goal 5: Immune-Related Disorders of the Bowel

Apply knowledge of immune system dysregulation to discuss specific immune-related disorders.

Objective GT5.1: Inflammatory Bowel Disease. Compare and contrast the pathophysiology and clinicopathological features of inflammatory bowel disease.

Objective GT5.2: Celiac Disease. Explain the pathophysiology of gliadin hypersensitivity (celiac disease).

Objective GT5.3: Crohn's Disease and Ulcerative Colitis. Describe the distribution of Crohn's disease, pathogenesis, and how transmural involvement is related to complications and compare and contrast Crohn's disease with ulcerative colitis

Learning Goal 6: Malabsorption

Apply knowledge of gastrointestinal anatomy and physiology to summarize the clinicopathologic features, diagnostic criteria, and therapy of disorders presenting with malabsorption.

Objective GT6.1: Systemic Disorders With Malabsorption. Compare and contrast the pathogenesis and clinicopathologic features of systemic disorders leading to malabsorption.

Objective GT6.2: Pancreaticobiliary Causes of Malabsorption. Outline disorders of the pancreas and bile acid metabolism, and discuss how they lead to malabsorption.

Objective GT6.3: Inflammatory Causes of Malabsorption. Explain how celiac disease, sprue, gastroenteritis, and inflammatory bowel disease lead to malabsorption.

Learning Goal 7: Bowel Infections

Apply knowledge of common pathogens and principles of immunity to describe the morphological features and clinical presentation of infectious diseases affecting immunocompetent and immunocompromised patients.

Objective GT7.1: Bowel Infections. Compare the underlying mechanism and clinicopathologic features of GI tract involvement by common bacterial, fungal, and parasitic pathogens.

Objective GT7.2: Helicobacter Infection. Relate the clinicopathologic features of *Helicobacter* to chronic gastritis and ulcer formation.

Learning Goal 8: Mechanical Disorders of Bowel

Apply knowledge of GI anatomy and physiology to explain the clinicopathologic features, diagnostic criteria, and therapy of disorders resulting in acid reflux, abnormal GI motility, and gastrointestinal tract obstruction.

Objective GT8.1: Dysphagia. Describe the pathophysiology and clinicopathological features of disorders presenting with dysphagia.

Objective GT8.2: Bowel Obstruction. Compare and contrast the pathophysiology of gastrointestinal disorders that present with GI obstruction, including disorders such as volvulus, hernias, adhesions, and intussusception.

Objective GT8.3: Diverticulosis. Describe the pathogenesis and complications of diverticulosis.

Objective GT8.4: Appendicitis. Describe the clinicopathologic features of acute appendicitis and discuss the clinical differential diagnosis and potential complications of this disorder.

Topic: Hepatobiliary (HB)

Hepatobiliary disorders resulting from abnormal development, genetic mutations, immune, infections, toxins, and intrinsic disease as they relate to liver and biliary abnormalities are enumerated.

Learning Goal 1: Hepatitis

Apply knowledge of pathogenic organisms infecting the liver and their transmission, natural history, pathogenesis, laboratory profiles, and histopathological patterns of injury to the prevention and diagnosis of hepatitis.

Objective HB1.1: Transmission of Hepatotropic Viruses. Explain the routes of transmission of different hepatotropic viruses and how they relate to the public health measures that have been implemented to prevent their transmission.

Objective HB1.2: Progression of Hepatitis. Compare and contrast the possible clinical outcomes of the major hepatotropic viruses with particular reference to the incidence of progression to chronic hepatitis and cirrhosis.

Objective HB1.3: Pathophysiology of Hepatitis. Describe the pathophysiology associated with the major hepatotropic viruses and explain how this knowledge can be used to assess the presence of hepatitis, and the management and prognosis of this disease.

Objective HB1.4: Histopathology of Hepatitis. Explain the pathogenetic mechanisms of injury that result in the histopathological findings observed in acute and chronic viral hepatitis.

Objective HB1.5: Hepatic Abscess. Describe the etiology of hepatic abscesses and the pathways that infectious agents may take to reach the liver.

Objective HB1.6: Cirrhosis. Classify types of cirrhosis, in terms of etiology, pathogenesis, morphologic pattern (gross and microscopic), and their relationship to neoplasia.

Learning Goal 2: Liver Toxins

Apply knowledge of the cellular response to injury, the pathogenic mechanisms leading to disease and the biochemical alterations of hepatic function to explain the clinicopathologic features, prognosis, and treatment of disorders resulting from ethanol and other drugs and toxins.

Objective HB2.1: Steatosis. Describe the clinicopathologic features of excessive ethanol ingestion, focusing on biochemical pathways and short- and long-term complications, and compare and contrast alcoholic with nonalcoholic fatty liver disease.

Objective HB2.2: Acetaminophen Toxicity. Describe the clinicopathologic features of excessive acetaminophen ingestion focusing on biochemical pathways and short- and long-term complications.

Objective HB2.3: Hemochromatosis. Discuss the clinicopathologic features of excessive iron absorption, focusing on biochemical pathways, genetic factors, and short- and long-term complications.

Learning Goal 3: Hepatic Neoplasms

Apply knowledge of the molecular basis of neoplasia to describe the clinical presentation, biologic behavior, morphologic appearance, classification, diagnosis, prognosis, and targeted therapy of hepatic neoplasms.

Objective HB3.1: Causes of Hepatocellular Carcinoma. Compare and contrast, in the context of geographic location, the epidemiological importance of the known etiologic agents associated with the development of hepatocellular carcinoma and suggest public health measures that might decrease its incidence.

Objective HB3.2: Pathogenesis. Discuss the pathogenesis of hepatocellular carcinoma arising in the setting of hepatitis B and hepatitis C, chronic hepatitis, and cirrhosis.

Objective HB3.3: Molecular Basis of Hepatic Adenoma. Describe how the molecular basis of a hepatic adenoma contributes to the risk of malignant transformation.

Objective HB3.4: Radiology of Cirrhosis. Identify the major space-occupying lesions that may be seen on radiographic imaging of the normal and cirrhotic liver, and discuss the complications of cirrhosis.

Objective HB3.5: Metastasis to the Liver. Describe the factors that lead to metastasis to the liver and the features of metastatic disease that distinguish it from primary neoplasms.

Learning Goal 4: Inflammatory and Congenital Hepatobiliary Disorders

Apply knowledge of the cellular response to injury, the pathogenic mechanisms leading to disease and the biochemical alterations of hepatic function to describe the clinicopathologic features, prognosis, and treatment of intrahepatic and extrahepatic biliary tract diseases.

Objective HB4.1: Inflammatory Disorders of the Liver. Outline how autoimmune hepatitis, primary and secondary biliary cirrhosis, and primary sclerosing cholangitis differ regarding associated conditions, incidence, sex predilection, etiology, laboratory features, clinical features and prognosis.

Objective HB4.2: Congenital Disorders of the Liver. Compare and contrast the etiology and treatment of biliary atresia and neonatal hepatitis.

Learning Goal 5: Molecular Basis of Biliary Neoplasia

Apply knowledge of the molecular basis of neoplasia to an understanding of the clinical presentation, biologic behavior, morphologic appearance, classification, diagnosis, prognosis, and targeted therapy of neoplasms involving the biliary tree.

Objective HB5.1: Extrahepatic Biliary Carcinoma. Describe the epidemiology, morphology, and clinical features of gallbladder and extrahepatic biliary tract carcinoma.

Objective HB5.2: Cholangiocarcinoma. Describe the presenting symptoms of cholangiocarcinoma and how the symptoms relate to the location.

Learning Goal 6: Nonneoplastic Disorders of Biliary Tree

Apply knowledge of both the embryonic principles of hepatic and bile tract development and mechanisms of fibroinflammatory injury to an understanding of disorders due to maldevelopment and acquired abnormalities of the biliary tree.

Objective HB6.1: Congenital Hepatic Fibrosis. Describe the inheritance, etiology, clinical and laboratory features, and prognosis of congenital hepatic fibrosis.

Objective HB6.2: Polycystic Liver Disease. Describe the inheritance, etiology, clinical and laboratory features, and prognosis of polycystic liver disease.

Learning Goal 7: Cholelithiasis

Apply knowledge of general biochemical principles to an understanding of how gallstones develop, risk factors for their development, and their clinical presentation and complications.

Objective HB7.1: Gallstones. Describe the risk factors, clinical features, complications, mechanisms, and composition of gallstones.

Objective HB7.2: Cholecystitis. Differentiate the epidemiology, morphology, clinical features, and complications of acute and chronic cholecystitis.

Objective HB7.3: Empyema and Hydrops of the Gallbladder. Differentiate the etiology, pathogenesis, morphology, and clinical features of empyema and hydrops of the gallbladder.

Topic: Pancreas (P)

Pancreas disorders resulting from abnormal development, genetic mutations, immune, infections and intrinsic disease as they relate to the exocrine pancreatic abnormalities are enumerated.

Learning Goal 1: Nonneoplastic Disorders of the Exocrine Pancreas

Apply knowledge of the structure and function of the pancreas to an understanding of the clinicopathologic features and diagnostic criteria of disorders resulting from cellular injury to the exocrine pancreas.

Objective P1.1: Pancreatitis. Compare and contrast acute and chronic pancreatitis in terms of etiology, pathogenesis, morphologic features, and complications.

Objective P1.2: Genetic Disorders of the Pancreas. Describe with examples genetic disorders that affect the function of the exocrine pancreas.

Learning Goal 2: Pancreatic Neoplasia

Apply knowledge of the molecular basis of neoplasia to an understanding of the clinical presentation, biologic behavior, morphologic appearance, classification, diagnosis, prognosis, and targeted therapy of pancreatic neoplasms.

Objective P2.1: Neoplasia of the Pancreas. Describe the major types of neoplasms affecting the exocrine pancreas.

Objective P2.2: Clinical Features of the Pancreatic Adenocarcinoma. Explain how the location of a pancreatic neoplasm determines its presenting symptoms and discuss the risk factors for pancreatic adenocarcinoma.

Objective P2.3: Endocrine Neoplasms of the Pancreas. Describe clinicopathological features of neoplasms of the endocrine pancreas.

Topic: Kidney (UTK)

Kidney disorders resulting from abnormal development, genetic mutations, immune, infections, and intrinsic disease as they relate to renal abnormalities are enumerated.

Learning Goal 1: Renal Neoplasia

Apply knowledge of the molecular basis of neoplasia to explain the clinical presentation, biologic behavior, morphologic appearance, classification, diagnosis, prognosis, and targeted therapy of renal neoplasms.

Objective UTK1.1: Renal Cell Carcinoma. Compare and contrast the 3 major types of renal cell carcinoma (clear cell, papillary, and chromophobe) in terms of clinical presentation, diagnostic morphological features, and molecular pathogenesis.

Objective UTK1.2: Urothelial and Renal Cell Carcinoma. Compare and contrast pelvic urothelial malignancies with renal cell carcinomas in relation to risk factors, microscopic appearance, and biological behavior.

Objective UTK1.3: Grading and Staging of Renal Carcinoma. Describe how renal cell carcinoma is graded and staged and discuss the factors that determine prognosis.

Objective UTK1.4: Wilms Tumor. Describe the clinical and pathologic features and molecular basis for Wilms tumor and list the histologic features that are important to recognize in determining prognosis, and the etiology of Wilms tumor as part of different syndromes.

Learning Goal 2: Structure and Function of the Nephron

Apply knowledge of kidney structure and function to summarize how acquired and hereditary abnormalities of the renal tubules and interstitium cause acute and/or chronic renal dysfunction.

Objective UTK2.1: Tubulointerstitial Diseases. Describe the clinicopathological features and pathogenesis of tubulointerstitial diseases and discuss how their pathogenesis relates to treatment and outcomes.

Objective UTK2.2: Nephritis. Compare and contrast acute pyelonephritis, drug-induced interstitial nephritis, and lupus nephritis in terms of pathogenesis, clinical presentation, histopathological appearance, and treatment.

Objective UTK2.3: Acute Tubular Injury. Compare and contrast ischemic and nephrotoxic forms of acute tubular injury, including typical clinical contexts, pathogenesis of renal failure, microscopic appearance, and expected outcome.

Objective UTK2.4: Chronic Inflammatory Injury. Compare and contrast chronic pyelonephritis and reflux nephropathy, including the organisms commonly associated with each.

Learning Goal 3: Renal Vascular Dysfunction

Compare and contrast the common causes of renal vascular dysfunction in terms of size and types of vessels involved, characteristic gross and microscopic morphology, pathogenesis, and clinical presentation.

Objective UTK3.1: Renal Artery Occlusion. Compare thrombotic and embolic causes of renal arterial occlusions in terms of underlying pathogenesis, gross and microscopic pathological anatomy, and clinical presentation.

Objective UTK3.2: Renal Changes in Hypertension. Discuss how the pathogenesis of hypertension leads to structural changes in the renal vasculature and how the characteristic pathological vascular lesions of the kidney seen in hypertension cause renal dysfunction.

Objective UTK3.3: HUS and TTP. Compare and contrast typical hemolytic uremic syndrome (HUS), atypical HUS, and thrombotic thrombocytopenic purpura (TTP) in terms of clinical presentation, renal histopathology, pathogenesis, and prognosis.

Learning Goal 4: Congenital Disorders of the Kidney

Apply knowledge of the embryologic principles of kidney and lower urinary tract development to explain developmental anomalies.

Objective UTK4.1: Inherited Renal Disorders. Compare autosomal dominant and autosomal recessive polycystic kidney disease in terms of pathological anatomy, molecular pathogenesis, and clinical presentation.

Learning Goal 5: Renal Syndromes

Apply knowledge of the structure and function of the kidney to describe the pathogenetic mechanisms, diagnostic criteria, and clinicopathologic features of glomerular diseases presenting with asymptomatic proteinuria, nephrotic and nephritic syndrome.

Objective UTK5.1: Nephritic Syndrome. Describe the proliferative and proinflammatory pathologies of conditions presenting with nephritic syndrome.

Objective UTK5.2: Nephrotic Syndrome. Describe the pathophysiology and morphologic features of nephrotic syndrome, and contrast with nephritic syndrome.

Objective UTK5.3: Immune-Mediated Renal Disease. Compare and contrast the mechanisms of immune complex and antibody-mediated glomerulonephritis.

Objective UTK5.4: Diabetic Nephropathy. Describe the pathogenesis of diabetic nephropathy and the associated clinicopathologic features.

Objective UTK5.5: Dysproteinemic Nephropathies. Describe the pathogenesis of the nephropathies associated with dysproteinemia.

Topic: Bladder (UTB)

Bladder disorders resulting from abnormal development, genetic mutations, infections, obstructions and intrinsic disease as they relate to urothelial abnormalities are enumerated.

Learning Goal 1: Bladder Neoplasia

Apply knowledge of the molecular basis of neoplasia to describe the clinical presentation, biologic behavior, morphologic appearance, classification, diagnosis, prognosis, and targeted therapy of bladder neoplasms.

Objective UTB1.1: Urothelial Carcinoma. Compare and contrast the different precursor lesions of urothelial carcinoma in terms of architecture, cytologic features, molecular–genetic changes, and propensity for invasion/progression.

Objective UTB1.2: Risk Factors for Urothelial Carcinoma. Relate the risk factors for urothelial carcinoma to general principles of carcinogenesis.

Objective UTB1.3: Diagnosis and Surveillance of Urothelial Carcinoma. Describe the typical clinical presentation of urothelial carcinoma and the advantages and limitations of urine cytology in diagnosis and surveillance of urothelial carcinoma.

Objective UTB1.4: Staging of Bladder Cancer. Relate stage of bladder cancer to prognosis and therapy, including the role of BCG, in the treatment of low-stage tumors.

Learning Goal 2: Bladder Infection

Apply knowledge of innate and adaptive immunity, pathogenic organisms infecting the bladder and their transmission to explain the natural history, pathogenesis, diagnosis, laboratory profiles, histopathological features, and prevention of cystitis.

Objective UTB2.1: Acute Cystitis. Discuss the typical clinical symptomatology of acute cystitis and the organisms commonly causing this disorder.

Objective UTB2.2: Noninfectious Cystitis. Describe the most common noninfectious causes of cystitis.

Objective UTB2.3: Cystitis Associated With Bladder Mass. Describe examples in which cystitis may result in mass lesions or morphologic lesions of the urinary bladder, and describe the pathogenesis of the process.

Learning Goal 3: Urinary Obstruction

Apply knowledge of the anatomy and physiology of the kidney to describe how disorders may lead to obstruction of urinary outflow.

Objective UTB3.1: Bladder Diverticula. Describe the pathogenesis of bladder diverticula, including congenital and acquired, and their potential role in infection, lithiasis, and obstruction and occult carcinoma.

Objective UTB3.2: Nephrolithiasis. List the different chemical types of nephrolithiasis, and explain the pathophysiologic mechanisms related to development and therapy/prevention of urinary stones.

Objective UTB3.3: Causes of Urinary Obstruction. Explain and give specific examples of several causes of urinary obstruction.

Topic: Male Reproductive—Prostate (MP)

Prostrate disorders resulting from genetic mutations, infections, and intrinsic disease as they relate to prostate abnormalities are enumerated.

Learning Goal 1: Prostate Neoplasia

Apply knowledge of the molecular and cellular origins of prostate cancers, specifically adenocarcinoma, to summarize the epidemiology, clinicopathological features, natural history, and treatment strategies for this disease.

Objective MP1.1: Prostate Adenocarcinoma. Outline the cellular phenotype of the typical adenocarcinoma cell and describe its molecular and immunohistochemical characteristics.

Objective MP1.2: Histopathologic Criteria for Prostate Adenocarcinoma. Define the histopathological diagnostic criteria for the diagnosis of adenocarcinoma.

Objective MP1.3: Epidemiology of Prostate Adenocarcinoma. Explain the epidemiology of prostate cancer with respect to age, race, and family history.

Objective MP1.4: "Histological" versus "Clinically Significant" Adenocarcinoma. Compare and contrast the significance of "histological" adenocarcinoma versus a "clinically significant" adenocarcinoma.

Learning Goal 2: Nonneoplastic Disorders of the Prostate

Apply knowledge of the molecular and cellular origins of nonneoplastic disorders of the prostate, specifically prostatitis and nodular hyperplasia, to explain the epidemiology, clinicopathological features, natural history, and treatment strategy for these diseases.

Objective MP2.1: Nodular Hyperplasia. Explain the molecular and hormonal origins of nodular hyperplasia, the area of the prostate affected, the natural history of the disease, various treatment strategies, and anticipated outcomes of treatment.

Objective MP2.2: Prostatitis. Describe the pathophysiologic basis for inflammatory conditions affecting the prostate, including the organisms causing this condition.

Topic: Male Reproductive—Testes (MT)

Testicular disorders resulting from abnormal development, germ cell lesions, infections, and intrinsic disease as they relate to testes abnormalities are enumerated.

Learning Goal 1: Nonneoplastic Disorders of the Testes

Apply knowledge of the molecular and cellular origins of nonneoplastic disorders of the testis to explain the epidemiology, clinicopathological features, natural history, and treatment strategy for these diseases.

Objective MT1.1: Cryptorchism. Name the structure through which the testes descend during fetal development and what is brought with the testes in the descent. Describe the complications observed for failure of the testes to descend (cryptorchidism).

Objective MT1.2: Testicular Torsion. Describe the clinicopathologic features that occur in the testis due to torsion of the spermatic cord.

Objective MT1.3: Orchitis. Discuss several inflammatory conditions affecting the testis and the clinicopathologic features associated with each.

Learning Goal 2: Testicular Neoplasia

Apply knowledge of the molecular and cellular origins of the common types of testicular cancer to explain the epidemiology, clinicopathological features, natural history, and treatment strategies for this disease.

Objective MT2.1: Germ-Cell Tumors of the Testis. Describe the most important risk factors for development of a germ cell tumor of the testis and outline the clinicopathologic features for the different morphologic patterns seen.

Objective MT2.2: Diagnosis of the Testicular Mass. Discuss a differential diagnosis for a testicular mass.

Topic: Breast (BR)

Breast disorders resulting from abnormal development, genetic mutations, immune mediated, infections, and intrinsic disease as they relate to breast abnormalities are enumerated.

Learning Goal 1: Nonneoplastic Disorders of the Breast

Apply knowledge of the embryology, cellular responses to injury, underlying etiology, and biologic and molecular alterations to describe the clinical presentation, inheritance risk, biologic behavior, morphologic appearance, classification, diagnosis, prognosis, and therapy of nonneoplastic disorders of the breast.

Objective BR1.1: Clinical Presentation of Breast Lesions. Identify the most frequently diagnosed breast lesions by age of the patient,

based on the most common clinical presentations in males versus females.

Objective BR1.2: Silicone Breast Implants. Discuss silicone breast implants in terms of the morphologic changes in the adjacent breast and the risk of subsequent autoimmune disease and cancer.

Objective BR1.3: Reactive Breast Conditions. Compare and contrast reactive breast conditions in terms of etiology, pathogenesis, morphology, and clinical features.

Objective BR1.4: Fibrocystic Change. Discuss the clinical significance of proliferative and nonproliferative fibrocystic change, with and without atypia, and describe how each of these changes and the family history affects the subsequent risk of developing breast cancer.

Learning Goal 2: Molecular Basis of Breast Neoplasms

Apply knowledge of the molecular basis of neoplasia to describe the clinical presentation, biologic behavior, morphologic appearance, classification, diagnosis, prognosis, and targeted therapy of breast neoplasms.

Objective BR2.1: Fibroadenoma and Phyllodes Tumor. Compare and contrast fibroadenoma and phyllodes tumor in terms of clinical features, morphologic findings, and prognosis.

Objective BR2.2: Precursors to Breast Carcinoma.. Describe the proposed precursor-carcinoma sequence in breast cancer and name the characteristic morphologic changes.

Objective BR2.3: Ductal Carcinoma-in-Situ. Compare and contrast ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) in terms of incidence, clinical presentation, morphology, biomarker expression, pattern of spread, natural history, treatment, and prognosis.

Objective BR2.4: Breast Cancer Susceptibility Genes. For the most common breast cancer susceptibility genes, describe the normal function of the gene product, incidence of gene mutation, reasons for its association with cancer, percentage of hereditary breast cancer, and risk of breast cancer by age 70.

Objective BR2.5: Gene Expression in Breast Cancer. Explain the major molecular classes of invasive ductal carcinoma of the breast identified by gene expression profiling, and describe how each correlates with prognosis and response to therapy.

Objective BR2.6: Categories of Breast Cancer. Construct a table to compare and contrast invasive ductal carcinoma (NOS), invasive lobular carcinoma, medullary carcinoma, colloid (mucinous) carcinoma, tubular carcinoma, and metaplastic carcinoma of the breast in terms of incidence, age predilection, etiology, pathogenesis, clinical presentation, gross and microscopic morphology, grade, molecular classification, patterns of spread, clinical course, prognostic indicators, treatment options, and survival rates, and indicate which are more common in males versus females.

Objective BR2.7: Factors Affecting Response and Prognosis of Breast Cancer. Explain the prognosis and likelihood of recurrence and response to therapy for breast cancer patients based on knowledge of molecular classification and/or gene expression profiling, morphologic classification, grade, prognostic marker studies, and other predictive factors.

Topic: Female Reproductive—Uterus (FU)

Uterine disorders resulting from abnormal development, genetic mutations, infections, and intrinsic disease as they relate to uterine abnormalities are enumerated.

Learning Goal 1: Uterine Neoplasia

Apply knowledge of the molecular basis of neoplasia to describe the clinical presentation, biologic behavior, morphologic appearance, classification, diagnosis, prognosis, and targeted therapy of uterine neoplasms.

Objective FU1.1: Clinical Features of Uterine Neoplasms. Compare and contrast common benign and malignant uterine neoplasms, including important clinicopathological features related to treatment and prognosis.

Objective FU1.2: Endometrial Carcinoma. Compare and contrast the precursors, clinical setting, risk factors, pathologic findings and prognosis for type I and type II carcinomas of the endometrium.

Objective FU1.3: Hereditary Colorectal Cancer and Endometrial Carcinoma. Discuss the relationship of endometrial carcinoma to hereditary nonpolyposis colorectal carcinoma.

Objective FU1.4: Smooth Muscle Tumors of the Uterus. Discuss the natural history, clinical presentation, and management of benign smooth muscle tumors of the uterus and the risk for malignant transformation.

Learning Goal 2: Nonneoplastic Uterine Disorders

Apply knowledge of uterine physiology, endocrinology, and anatomy to compare and contrast the clinical presentation and pathology of common nonneoplastic uterine disorders.

Objective FU2.1: Endometrial Hyperplasia. Define endometrial hyperplasia and discuss its etiology, classification, and prognosis.

Objective FU2.2: Menstrual Cycle. Identify the phases of the menstrual cycle and the major hormonal changes that occur, comparing normal menstruation to common causes of abnormal bleeding in adolescents, perimenopausal, and postmenopausal women.

Objective FU2.3: Uterine Adenomyosis. Compare and contrast the pathology of adenomyosis with endometriosis.

Objective FU2.4: Abnormal Uterine Bleeding. Discuss causes of abnormal uterine bleeding including hormonal disturbances, acute and chronic endometritis, and endometrial polyps.

Learning Goal 3: Cervical Disorders

Apply knowledge of cervical physiology and anatomy to compare and contrast the clinical presentation and pathology of common cervical disorders.

Objective FU3.1: Clinical Features of Cervical Dysplasia and Neoplasms. Discuss the common human papillomavirus (HPV) types that affect the cervix and discuss the pathogenesis of cervical dysplasia and neoplasia, and cervical screening methods and prevention.

Learning Goal 4: Female Genital Tract

Apply knowledge of physiology and anatomy to compare and contrast the clinical presentation and pathology of common female genital tract disorders.

Objective FU4.1: Clinical Features of Pelvic Infections. Discuss the common pelvic infections including those affecting the vulva, vagina, cervix, and fallopian tubes, and describe the pathogenesis of pelvic inflammatory disease, common organisms involved, and its complications.

Topic: Female Reproductive—Ovary (FO)

Ovarian disorders resulting from abnormal development, genetic mutations, infections, immune, and intrinsic disease as they relate to the ovary are enumerated.

Learning Goal 1: Ovarian Neoplasia

Apply knowledge of the molecular basis of neoplasia to describe the clinical presentation, biologic behavior, morphologic appearance, classification, diagnosis, prognosis, and targeted therapy of ovarian neoplasms

Objective FO1.1: Ovarian Development. Describe the embryologic development and the histologic components of the ovary, including surface Müllerian epithelium, germ cells, and the sex-cord stromal cells.

Objective FO1.2: Causes of Ovarian Neoplasm. Describe the risk factors, genetic associations, and molecular basis, including hereditary cancer syndromes, for ovarian neoplasms, including those derived from epithelium, sex-cord stromal as well as germ cell neoplasms.

Learning Goal 2: Nonneoplastic Disorders of the Ovary

Apply knowledge of infectious diseases, embryology, and immunology to explain the major pathologic features of processes affecting the ovary.

Objective FO2.1: Infections Involving the Ovary. Describe the pathogens, bacterial, fungal, and parasitic that can cause ovarian disease and explain the underlying mechanisms, clinicopathologic features, and complications.

Objective FO2.2: Polycystic Ovary Syndrome. Explain the pathophysiologic basis of polycystic ovary syndrome.

Objective FO2.3: Immune Diseases of the Ovary. Explain the mechanism(s) by which the dysregulation of the immune system gives rise to ovarian disease and describe the pathology observed.

Objective FO2.4: Menopause. Describe the clinicopathologic features of menopause and the basis for treatment.

Topic: Female Reproductive—Disorders of Pregnancy (FDP)

Pregnancy disorders resulting from abnormal implantation, genetic mutations, hemodynamic, immune, infections, and intrinsic disease as they relate to gestational disease abnormalities are enumerated.

Learning Goal 1: Disorders of Pregnancy

Apply knowledge of embryology, cellular responses to injury, hemodynamics, and molecular alterations to summarize the clinical presentation, morphologic appearance, classification, diagnosis, biologic behavior of and therapy for disorders of pregnancy.

Objective FDP1.1: Ectopic Pregnancy. Describe risk factors, characteristic morphologic findings, potential outcomes, and the medical/surgical options for management of ectopic pregnancy in relation to the pathogenesis and likelihood of adverse consequences.

Objective FDP1.2: Spontaneous Abortion. List 2 fetal and 6 maternal causes for spontaneous abortion and indicate which is the most common.

Objective FDP1.3: Late Pregnancy. Describe how disorders of late pregnancy can lead to effects that threaten the mother and/or fetus.

Objective FDP1.4: Infections during Pregnancy. Discuss the ascending and hematogenous infections occurring during pregnancy in terms of etiology, pathogenesis, morphology, methods of diagnosis, prognosis, and treatment.

Objective FDP1.5: Eclampsia. Explain the principal pathophysiologic aberrations of the placenta and maternal circulation in preeclampsia and eclampsia; the characteristic morphologic features in the placenta, liver, kidney, and brain; and how management is affected by gestational age and severity of disease.

Objective FDP1.6: Gestational Trophoblastic Disease. Explain with specific examples how to differentiate forms of gestational trophoblastic disease based on etiology, pathogenesis, morphologic features, clinical features, and laboratory findings,

including potential consequences and/or subsequent risks, treatment, and prognosis for each.

Objective FDP1.7: Gestational Diabetes. Describe the pathophysiologic effects of diabetes mellitus on the mother and fetus.

Topic: Endocrine (EN)

Endocrine disorders resulting from abnormal development, genetic mutations, immune, infections, and intrinsic disease as they relate to multiple endocrine organ abnormalities are enumerated.

Learning Goal 1: Hyper- and Hypopituitarism

Apply knowledge of pituitary physiology to describe the pathophysiology and clinicopathologic features of disorders associated with hyperpituitarism and hypopituitarism.

Objective EN1.1: Anterior Pituitary. List several causes for destruction of the anterior pituitary and the clinicopathologic features associated with each.

Objective EN1.2: Sheehan's Syndrome. Define Sheehan's syndrome and discuss the clinicopathologic features associated with it.

Objective EN1.3: Posterior Pituitary. Outline the clinicopathologic features associated with disorders affecting the posterior pituitary gland.

Learning Goal 2: Hyper- and Hypothyroidism

Apply knowledge of thyroid physiology to explain the pathophysiology and clinicopathologic features of disorders associated with hyperthyroidism and hypothyroidism.

Objective EN2.1: Causes of Hyper- and Hypothyroidism. Compare and contrast the causes of hyperthyroidism versus hypothyroidism.

Objective EN2.2: Clinical Features of Hyper- and Hypothyroidism. Compare and contrast the clinicopathologic features of hyperthyroidism versus hypothyroidism.

Learning Goal 3: Autoimmune Thyroiditis

Apply knowledge of immune system dysregulation to summarize immune-related disorders of the thyroid.

Objective EN3.1: Graves' Disease, Hashimoto Thyroiditis, and Subacute Thyroiditis. Compare and contrast the pathophysiology and clinicopathologic features of Graves' disease, Hashimoto's thyroiditis, and subacute lymphocytic thyroiditis.

Objective EN3.2: Granulomatous Thyroiditis. Compare and contrast immune-mediated thyroid disease with subacute granulomatous thyroiditis (de Quervain's thyroiditis).

Learning Goal 4: Hyper- and Hypoadrenalism

Apply knowledge of adrenal physiology to describe the pathophysiology and clinicopathologic features of disorders associated with adrenocortical hyperfunction (hyperadrenalism) and adrenocortical insufficiency.

Objective EN4.1: Cushing Syndrome. Compare and contrast the causes and clinicopathologic features of hypercortisolism (Cushing syndrome) and the pathophysiologic basis distinguishing between these causes and the management of this disease.

Objective EN4.2: Hyperaldosteronism. Compare and contrast the causes and clinicopathologic features of primary and secondary hyperaldosteronism.

Objective EN4.3: Congenital Adrenal Hyperplasia. Outline the clinicopathologic features of congenital adrenal hyperplasia.

Objective EN4.4: Adrenocortical Insufficiency. Compare and contrast the causes of adrenocortical insufficiency, including the pathogenesis of primary acute and chronic adrenocortical insufficiency.

Learning Goal 5: Endocrine Neoplasms

Apply knowledge of the molecular basis of neoplasia to explain the clinical presentation, biologic behavior, morphologic appearance, classification, diagnosis, prognosis, and targeted therapy of endocrine neoplasms.

Objective EN5.1: Thyroid Neoplasms. Compare and contrast the clinicopathologic features of follicular adenomas, follicular carcinoma, and papillary thyroid carcinoma.

Objective EN5.2: Medullary Thyroid Carcinoma. Describe the molecular basis and clinicopathologic features of medullary thyroid carcinoma.

Objective EN5.3: Pheochromocytoma and Paraganglioma. Outline the clinicopathologic features of pheochromocytoma and compare and contrast the hereditary cancer syndromes associated with paragangliomas/pheochromocytomas.

Objective EN5.4: Pituitary Adenoma. Explain the clinicopathologic features of pituitary adenomas including their genetic mutations and their associated clinical syndromes.

Objective EN5.5: Endocrine Neoplasia of the Pancreas including Islet Cell Tumors. Compare and contrast the clinicopathologic features of the pancreatic endocrine tumors including the genetic alterations and complications of each.

Learning Goal 6: Endocrine Pancreas

Apply knowledge of the structure and function of the endocrine pancreas and biochemical principles of carbohydrate metabolism to summarize the clinicopathologic features, diagnostic criteria, and therapy of disorders resulting from excess or decreased production of insulin and other islet cell hormones.

Objective EN6.1: Features of Diabetes Mellitus. Compare and contrast the clinicopathologic features of type 1 and type 2 diabetes.

Objective EN6.2: Complications of Diabetes Mellitus. Outline the pathologic complications of diabetes mellitus.

Objective EN6.3: Multiple Endocrine Neoplasia (MEN) Syndromes. Compare and contrast the clinicopathologic features of MEN 1 with MEN 2 and 3.

Topic: Skin (SK)

Skin disorders resulting from abnormal development, genetic mutations, immune, infections, and intrinsic disease as they relate to dermal abnormalities are enumerated.

Learning Goal 1: Classification of Skin Disease

Apply knowledge of histology, cell biology, inflammation, and neoplasia to an understanding of the clinical presentation, biologic behavior, morphologic appearance, and classification of diseases of the skin.

Objective SK1.1: Pathophysiology of Changes in the Skin. Describe the pathophysiologic basis for changes in the color, surface texture, swelling, temperature, and sensitivity of skin.

Learning Goal 2: Infections of the Skin

Apply knowledge of the anatomic and immunologic structure of the skin to discuss the role of skin in protecting against direct invasion of skin and appendages by pathogens.

Objective SK2.1: Barrier Function of Skin. Explain the anatomic basis for the skin as a barrier and the role of normal flora that colonize the skin in this function.

Objective SK2.2: Cutaneous Infections. Describe common bacterial, viral, fungal, and parasitic agents that may cause cutaneous infections and the particular sites that they infect, and morphologic features and complications of these infections.

Learning Goal 3: Immune-Related Disorders of the Skin

Apply knowledge of basic concepts in immunopathology and the key immunologic functions of components of the skin to understand the pathologic basis of disease caused by reactivity to exogenous agents versus immunologically driven disease with a genetic component.

Objective SK3.1: Manifestations of Exogenous Antigens. Describe the clinical features and pathologic basis for skin manifestations to exogenous antigens including infectious organisms, drugs, chemicals, and environmental agents.

Objective SK3.2: Immune Diseases of the Skin. Describe the clinical features and pathologic basis for the following immunologically driven diseases with a genetic component: eczema, psoriasis, and vitiligo.

Learning Goal 4: Inherited Disorders of the Skin

Apply knowledge of genetics, skin structure, and function and basic principles of pathology to an understanding of nonneoplastic inherited disorders of the skin.

Objective SK4.1: Inherited Blistering Diseases. Describe the genetic basis for blistering diseases affecting the skin.

Learning Goal 5: Skin Neoplasia

Apply knowledge of the molecular basis of neoplasia to an understanding of the clinical presentation, biologic behavior, morphologic appearance, classification, diagnosis, prognosis, and therapy of benign and malignant skin neoplasms.

Objective SK5.1: Benign Skin Neoplasms. Describe the clinical presentation and histopathologic findings of benign skin growths of the following cellular origins: basal cell, squamous cell, melanocytes, as well as neoplasms of dermal origin.

Objective SK5.2: Malignant Skin Neoplasms. Describe the clinical presentation, precursor lesions, risk factors and hereditary cancer syndromes that lead to the following skin cancers: basal cell carcinomas, squamous cell carcinoma, and melanoma.

Objective SK5.3: Genetic Disorders Predisposing to Skin Cancer. Identify the genetic disorders with high risk of skin cancers and explain the molecular basis of that risk as well as the genomic mutations involved.

Objective SK5.4: Sun Exposure. Explain the role of ultraviolet light and other environmental factors in development of various skin cancers.

Objective SK5.5: Cutaneous T-Cell Lymphomas. Describe the various clinical presentations of cutaneous T-cell lymphoma/mycosis fungoides and discuss the natural course of the disease.

Topic: Musculoskeletal System (MS)

Musculoskeletal disorders resulting from abnormal development, genetic mutations, nutritional, immune, infections, and intrinsic disease as they relate to lung abnormalities are enumerated.

Learning Goal 1: Bone Neoplasia

Apply knowledge of the molecular basis of neoplasia to describe the clinical presentation, biologic behavior, morphologic appearance, classification, diagnosis, prognosis, and targeted therapy of bone neoplasms.

Objective MS1.1: Categories of Bone Tumors. Describe examples of bone forming, cartilage forming, and other common bone tumors including the clinicopathologic features, radiological features, treatment, and prognosis of each.

Objective MS1.2: Bone-Forming Sarcomas in Children. Describe the most common benign and malignant bone forming tumors in

children and adolescents in terms of clinical presentation, radiologic findings, histologic features, treatment, and prognosis.

Objective MS1.3: Cartilage-Forming Sarcomas. Describe the most common benign and malignant cartilaginous tumor of bone in children and adolescents in terms of clinical presentation, radiologic findings, histologic features, treatment, and prognosis.

Objective MS1.4: Metastatic Tumors. Describe the tumors that commonly metastasize to bone, the radiologic manifestations of metastatic lesion involving bone, and the difference between osteoblastic and osteolytic metastases.

Objective MS1.5: Soft-Tissue Tumors. Describe the common benign and malignant soft tissue tumors including the genetic contribution to tumor development and progression.

Learning Goal 2: Nonneoplastic Disorders of the Musculoskeletal System

Apply knowledge of histology, immunology, microbiology, and biological and molecular alterations to discuss clinical presentation, biological behavior, morphological appearance, and natural history of nonneoplastic disorders of bones, joints, and skeletal muscle.

Objective MS2.1: Osteomalacia and Rickets. Compare and contrast osteomalacia and rickets with respect to pathogenesis and clinicopathologic features.

Objective MS2.2: Osteomyelitis. Discuss the pathogenesis of osteomyelitis, including predisposing factors, organisms involved, morphologic appearance, and complications.

Objective MS2.3: Osteoporosis. Distinguish primary from secondary osteoporosis in terms of etiology, pathogenesis, and morphology.

Objective MS2.4: Spinal Degenerative Disease. Describe the common degenerative diseases of the spine.

Objective MS2.5: Pathologic Fracture. Compare and contrast pathologic versus nonpathologic fractures including the potential for healing.

Objective MS2.6: Paget Disease. Discuss the clincopathologic changes of Paget Disease including the histologic phases, genetic changes, and complications of this disorder.

Objective MS2.7: Arthritis. Compare and contrast rheumatoid and osteoarthritis including the etiology, pathogenesis, and morphology of each.

Topic: Nervous System—Central Nervous System (NSC)

Nervous system disorders resulting from abnormal development, genetic mutations, vascular, immune, infections, and intrinsic disease as they relate to central nervous system (CNS) abnormalities are enumerated.

Learning Goal 1: CNS Neoplasia

Apply knowledge of the pathological and molecular basis of common brain tumors to describe their clinical behavior, effects on the nervous system, and therapies.

Objective NSC1.1: Features of Brain Tumors. Explain the pathophysiology underlying the signs and symptoms associated with brain tumors.

Objective NSC1.2: Classification of Brain Tumors. Compare and contrast the common types of brain tumors that affect the cerebrum, the cerebellum, the meninges, and the cranial nerves in adults and children; and outline their molecular basis and clinicopathologic features.

Objective NSC1.3: Hereditary Tumor Syndromes. Describe the major hereditary tumor syndromes of the central nervous system, the genes responsible for each syndrome, and the spectrum of tumors associated with each syndrome.

Objective NSC1.4: Grading of Brain Tumors. Explain the pathophysiologic basis for grading primary brain tumors and discuss how grading relates to prognosis and governs patient management.

Objective NSC1.5: Complications of Brain Tumors. Describe several complications of brain tumors and give specific examples.

Objective NSC1.6: Carcinomas Metastasizing to the CNS. Discuss carcinomas that commonly metastasize to the central nervous system and describe the locations in which metastases may be seen.

Learning Goal 2: Infection

Apply knowledge of clinical features, neuroimaging studies and location of lesion(s) to develop a differential diagnosis for CNS infection.

Objective NSC2.1: Infections of the CNS. Compare and contrast the clinical, gross, and microscopic manifestations of common bacterial, viral, and fungal infections of the central nervous system.

Objective NSC2.2: Opportunistic Infections of the CNS. Discuss 5 common opportunistic infections that involve the CNS of immunocompromised individuals and describe their pathologic features.

Objective NSC2.3: Progressive Multifocal Leukoencephalopathy. Describe the clinicopathologic features of progressive multifocal leukoencephalopathy (John Cunningham virus) and contrast them with infiltrative astrocytoma.

Objective NSC2.4: Suppurative Meningitis and Abscess. Describe the gross and microscopic features of acute suppurative meningitis and brain abscess; and name the organisms most commonly associated with each.

Learning Goal 3: Spinal Cord Disorders

Apply knowledge of neuroanatomy, pathogenesis, and biologic behavior to develop differential diagnoses and determine appropriate therapy for disorders of the spinal cord.

Objective NSC3.1: Ependymoma. Describe the importance of distinguishing ependymoma from infiltrative astrocytoma intraoperatively and list the histologic features of each.

Objective NSC3.2: Spinal Findings in Demyelinating and Neuromuscular Disorders. Explain how examination of a spinal cord at autopsy is important for the diagnosis and classification of demyelinating and/or neuromuscular diseases.

Objective NSC3.3: Multiple Sclerosis. Describe the pathogenesis, clinical presentation, and gross and microscopic pathologic features of multiple sclerosis.

Learning Goal 4: Neuromuscular Disorders

Apply knowledge of clinical, anatomic, and neuropathologic principles to the diagnosis of neuromuscular disorders.

Objective NSC4.1: Amyotrophic Lateral Sclerosis. Describe the etiology, pathogenesis, and clinical features of amyotrophic lateral sclerosis.

Objective NSC4.2: Mitochondrial Disorders. Describe the etiology, pathogenesis, and clinical features of 2 types of mitochondrial diseases affecting muscle, and explain why it may be important to obtain fresh frozen muscle to aid diagnosis.

Learning Goal 5: Dementia

Apply knowledge of structure and function and general pathologic concepts to describe disorders where dementia is a component.

Objective NSC5.1: Amyloid and Tau in Dementia. Define the essential underlying abnormalities of amyloid and tau proteins in the most common causes of dementia in the United States.

Objective NSC5.2: Abnormal Protein Processing in Neurodegenerative Disease. Describe the protein processing abnormalities responsible for multiple neurodegenerative diseases.

Objective NSC5.3: Alzheimer's Disease. Describe the clinical features, gross pathology, and histopathology of Alzheimer's disease and name 3 regions of the brain that are usually involved.

Objective NSC5.4: Genes Implicated in Alzheimer's Disease. Discuss 3 genes in which mutations have been identified in patients with early onset Alzheimer's disease.

Objective NSC5.5: Disorders of the Basal Ganglia. Describe several diseases which involve the basal ganglia and describe how to distinguish among the diseases in terms of gross, microscopic, and clinical pathology.

Learning Goal 6: Demyelinating Disorders

Apply knowledge of the structure and function of the brain and general immunopathology concepts to summarize disorders that result in demyelination in terms of their etiology, pathogenesis, clinical and morphologic features, natural history, and therapeutic options.

Objective NSC6.1: Autoimmune Mechanisms in MS. Describe the autoimmune mechanism mediated by CD4+ T cells that react against self myelin antigens in multiple sclerosis and outline the clinicopathologic features of the disease.

Learning Goal 7: Ischemia of the Brain

Apply knowledge of the structure and function of the brain and general pathology concepts to discuss disorders resulting from altered blood supply and hypoxia to the brain.

Objective NSC7.1: Stroke. Compare and contrast the 2 major mechanisms for stroke and how treatment differs for each.

Objective NSC7.2: Traumatic Brain Injury. Describe the pathologic findings seen in the most common causes of traumatic brain injury.

Objective NSC7.3: Cranial Hemorrhage. Compare and contrast the etiologies and clinical presentations of epidural, subdural, subarachnoid hemorrhages, basal ganglionic, and lobar hemorrhages.

Objective NSC7.4: Hypertensive Hemorrhage. Describe the mechanism of hypertensive hemorrhage and name 3 common locations in which this occurs.

Objective NSC7.5: Embolic Infarction. Describe how embolic infarcts differ from atherothrombotic infarcts in pathologic appearance and name 3 sources of emboli.

Objective NSC7.6: Acute Versus Chronic Brain Injury. Compare and contrast the gross and histopathologic appearance of acute versus remote brain infarction.

Topic: Nervous System—Peripheral Nervous System and Eye (NSP)

Nervous system disorders resulting from abnormal development, genetic mutations, vascular, immune, infections and intrinsic disease as they relate to peripheral nervous system (PNS) and ocular abnormalities are enumerated.

Learning Goal 1: Peripheral Nerve Disorders

Apply knowledge of the structure and function of the peripheral nerves and general pathology concepts to discuss peripheral nerve disorders.

Objective NSP1.1: Neuromuscular Junction Disorders. Describe the clinicopathologic features of antibody-mediated disorders of

the neuromuscular junction such as myasthenia gravis and Lambert-Eaton myasthenic Syndrome.

Objective NSP1.2: Neuropathy. Compare and contrast the clinicopathologic features of inflammatory neuropathies, autoimmune neuropathy, and infectious neuropathy.

Objective NSP1.3: Neurofibromatosis. Compare and contrast the clinicopathologic features of neurofibromatosis types 1 and 2.

Learning Goal 2: PNS Neoplasia

Apply knowledge of the pathological and molecular basis of common PNS tumors to describe their clinical behavior, effects on the nervous system, and therapies.

Objective NSP2.1: Hereditary Tumor Syndromes. Describe the major hereditary tumor syndromes of the peripheral nervous system, the genes responsible for each syndrome, and the spectrum of tumors, including the histology associated with each syndrome.

Objective NSP2.2: Tumors of the Peripheral Nervous System. Compare and contrast the common benign from malignant PNS tumors, and outline their molecular basis and clinicopathologic features.

Learning Goal 3: Ocular Disorders

Apply knowledge of the structure and function of the eye and general pathology concepts to discuss common ocular disorders.

Objective NSP3.1: Ocular Disorders. Describe the clinicopathologic features of common primary and secondary disorders of the eye including macular degeneration and uveitis.

Objective NSP3.2: Ocular Neoplasm. Describe the clinicopathologic features of common neoplasms of the eye including ocular melanoma and retinoblastoma.

Competency 3

Diagnostic Medicine and Therapeutic Pathology

Diagnosis and patient management require the student to apply their knowledge of disease mechanisms and organ system pathology to achieve efficient and effective use of clinical laboratory testing. In addition, the student should learn the proper use of blood/blood product utilization to enable optional diagnosis, treatment, and patient care.

There are 10 topics within this competency area. Each topic includes general learning goals and specific objectives that medical students should be able to meet upon graduation from medical school. Table 3 lists the topic areas and shows the number of goals and objectives for each.

Table 3. Diagnostic Medicine and Therapeutic Pathology.

Topic	Number of Goals	Number of Objectives	Reference Code
General principles	1	10	GP
Transfusion medicine	1	6	TM
Hematology	4	20	H
Microbiology	6	32	M
Chemistry	1	8	CHEM
Immunology	1	4	IMM
Genomics	5	20	GE
Autopsy	3	9	AU
Surgical pathology	5	10	SP
Cytopathology	2	7	CYP

Topic: General Principles (GP)

Every physician should have an appreciation for the preanalytical, analytical, and postanalytical phases of laboratory testing. In addition, physicians need an appreciation of the statistical treatment of data that underlies test utilization. This includes but is not limited to the ability to choose the correct test to make a diagnosis enabling treatment selection and to employ the appropriate testing paradigm to monitor patients with chronic diseases enabling optimal clinical management.

Learning Goal 1: Laboratory Tests

Apply knowledge of clinical medicine, pathology, and statistics to determine the utility of a laboratory test in making a diagnosis and in monitoring chronic disease management. Explain the interpretation and limitations of clinical laboratory assays.

Objective GP1.1: Pre- and Postanalytical Errors. Give examples of common sources of preanalytical and postanalytical errors and categorize errors when the following procedures are not properly followed: pairing patient/specimen identification with the requisition forms, using correct specimen containers/tubes for specific tests, and timing of collection, transport, and storage.

Objective GP1.2: Sensitivity and Specificity. Evaluate the quality of an assay in differentiating disease versus nondisease states, including graphically presenting and interpreting the data. Determine the relationship between sensitivity and specificity for this assay.

Objective GP1.3: Pretest Probability. Determine the value of an assay by evaluating the impact of differing pretest probabilities such as prevalence on the positive and negative predictive value of the test. Give examples of the laboratory tests used

to evaluate clinical disorders where predictive values are used to develop screening, diagnostic, prognostic, and patient management protocols.

Objective GP1.4: Reference Intervals. Describe the methods used to establish reference intervals and how the following conditions apply: the effect of demographics, treatments, or disease states on reference intervals variability; the difference between reference ranges and therapeutic ranges and why 5% of laboratory test results fall outside a reference range; analytical versus clinical sensitivity; and mixing test results in the clinical information system from different laboratories that use different methodologies.

Objective GP1.5: Test Variability. Explain the difference between technical variability and biologic variability including how physical and chemical parameters, such as sample size, hemolysis, and lipemia, can affect test results. Define analytical uncertainty, precision, accuracy, and coefficient of variation, and describe factors that contribute to each.

Objective GP1.6: Turn-around Time. Compare and contrast appropriate uses of "stat" and "routine" test priorities with discussion of critical values and the elements of "turn-around time." Predict which elements affect turn-around time the most.

Objective GP1.7: Regulatory Issues. Explain the broad differences between Food and Drug Administration (FDA)-approved tests and laboratory-developed tests, including Clinical Laboratory Improvement Amendments (CLIA) waived and nonwaived tests, and discuss the regulatory issues involved in physician-office laboratories, home testing, and provider-performed microscopy.

Objective GP1.8: Point-of-Care Testing. Explain how "point-of-care" (POC) testing in the physician office, multispecialty clinic, and hospital can enable better patient and population management of acute and chronic disease and why values generated using POC methods could differ from values generated in a high-throughput laboratory.

Objective GP1.9: Test Utilization. Create a clinical scenario that begins with a patient diagnosis and monitors a chronic disease for years, taking into account the following aspects: a laboratory testing decision tree to make the diagnosis, a protocol for monitoring the patient, the use of test panels and individual tests, the impact on healthcare cost for overutilization of laboratory testing, and the potential impact on cost for underutilization both at the diagnostic stage and in the management of chronic disease.

Objective GP1.10 Test Economics. Compare and contrast the cost of several common laboratory diagnostic tests, such as Complete Blood Count (CBC) and CBC with a manual differential. Discuss the cost of diagnostic testing and the impact on healthcare costs.

Topic: Transfusion Medicine (TM)

Every physician needs an understanding of transfusion medicine which encompasses the transfusion of red blood cells, platelets, and plasma products in order to correct deficiencies in patients or remove offending antibodies. Transfusions are not without risk and knowledge of the pathophysiology of the disease and risks of transfusion are vital for physicians for optimal patient outcomes.

Learning Goal 1: Concepts of Blood Transfusion

Apply knowledge of pathology, hematopoietic cell physiology and immunology to explain concepts of blood component transfusion and the therapeutic interventions in transfusion medicine.

Objective TM1.1: Blood Components. Define the blood components and blood component substitutes available for clinical use; the evidence-based indications and dosing for transfusion of these components; and how the efficacy of transfusion may be monitored.

Objective TM1.2: Transfusion Reactions. Compare and contrast the pathophysiology, presentations, prophylaxis, and acute management of the different types of transfusion reactions.

Objective TM1.3: Infectious Risks. Discuss infectious disease risks of transfusion.

Objective TM1.4: HLA. Explain the HLA system and its role in both transfusion and transplantation.

Objective TM1.5: Apheresis. Explain the clinical role of therapeutic apheresis in the management of the following disorders: sickle cell anemia, thrombotic thrombocytopenia, acute and chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, antiglomerular basement membrane disease, organ transplantation, plasma cell dyscrasias, leukemia, and lymphoma.

Objective TM1.6: Paternity Testing. Explain the role of blood group testing in determining paternity identification.

Topic: Hematology (H)

Every physician needs a thorough understanding of one of the most common tests ordered from the laboratory, the complete blood count or CBC. Differentiating between tests needed for diagnosis and treatment of anemias and coagulation disorders is important for appropriate treatment and monitoring of these disorders.

Learning Goal 1: Normal Coagulation

Apply knowledge of biochemistry, pharmacology, and pathology to describe the basic cellular and molecular events associated with blood coagulation and explain laboratory tests for diagnosis and management of coagulation disorders.

Objective H1.1: Platelet Aggregation After Injury. Describe the process whereby platelets are activated and aggregate after blood vessel injury.

Objective H1.2: Platelet Inhibitors. Explain the action and the clinical use of common platelet function inhibitor drugs including, but not limited to, aspirin and clopidogrel.

Objective H1.3: Coagulation Cascade. Describe the process of fibrin formation in terms of the initiation of coagulation reactions by the exposure of tissue factor and/or "contact activation" and the subsequent proteolytic interactions that involve coagulation factor proteins.

Objective H1.4: Anticoagulants. Explain the actions and clinical use of commonly used anticoagulants including warfarin, the heparins, and the new oral direct inhibitors of thrombin and factor Xa.

Learning Goal 2: Diagnosis and Management of Coagulation Disorders

Apply knowledge of biochemistry, pharmacology, and pathology to describe the use of specific laboratory tests to diagnose and manage coagulation disorders.

Objective H2.1: Monitoring Anticoagulation Therapy. Explain selection of appropriate tests for identifying the cause(s) of bleeding and to monitor therapeutic anticoagulation.

Objective H2.2: Platelet Function Testing. Explain platelet function testing and discuss how platelet function testing can be used to differentiate between disorders of low platelets versus abnormal function of platelets.

Objective H2.3: Clotting Factor Deficiencies. Identify the likely deficiency of clotting factor(s) using the prothrombin time and the partial thromboplastin time coagulation tests.

Objective H2.4: Evaluations of Coagulopathies. Compare and contrast the roles of the following in evaluating coagulopathies: clinical history, prothrombin time test, partial thromboplastin time test, D-dimer assay, platelet count, and platelet function tests.

Objective H2.5: Evaluation of the Bleeding Patient. Describe how to evaluate a bleeding patient with a hemorrhagic disorder, and explain how the history influences testing, including the uses and limitations of screening PT, PTT, and platelet counts.

Objective H2.6: Disseminated Intravascular Coagulation. Explain how bleeding occurs in patients with disseminated intravascular coagulation and in patients with severe liver disease using coagulation testing.

Objective H2.7: Hereditary and Acquired Causes of Thrombosis. Describe the major hereditary and acquired risk factors for thrombosis and how coagulation testing is used to confirm the diagnosis.

Learning Goal 3: Mechanisms of Anemia

Apply knowledge of red blood cell (RBC) structure/function and nutrient metabolism, the mechanisms of anemia, and the clinical and pathological features of common causes of anemia, to develop an appropriate differential diagnosis.

Objective H3.1: RBC Function. Summarize laboratory testing for key cellular structures and functions of the RBC.

Objective H3.2: Nutrients Required for Erythropoiesis. Discuss the laboratory testing for specific nutrients including iron and vitamins to erythropoiesis.

Objective H3.3: Blood Loss. Differentiate between the pathophysiology of acute and chronic blood loss.

Learning Goal 4: Diagnosis of the Anemic Patient

Apply knowledge of RBC structure/function and nutrient metabolism, the mechanisms of anemia, and the clinical and pathological features of common causes of anemia, to develop a diagnostic decision tree and recommend appropriate intervention for a patient with anemia.

Objective H4.1: Causes and Diagnosis of Anemia. Describe the primary causes of anemia, compare and contrast the clinical features and mechanisms of each, and discuss the different testing strategies for normocytic, macrocytic, and microcytic anemia.

Objective H4.2: Interpreting the CBC. Use the CBC and explain the contribution of each of the measurements of the CBC, how they are derived, and how they can help diagnose blood cell disorders using specific examples.

Objective H4.3: Peripheral Smear Evaluation in Anemia. Discuss the RBC and white blood cell morphology on a peripheral smear to develop a differential diagnosis for a patient with anemia.

Objective H4.4: Inherited Anemia. Correlate the genetic, pathological, and clinical features in patients with common inherited anemias.

Objective H4.5: Acquired Anemia. Compare and contrast the clinical features and pathophysiology acquired including mechanical trauma, toxic, and antibody-mediated anemias.

Objective H4.6: Treatment of Anemia. Discuss when specific interventions should and should not be used for patients with specific types of anemia.

Topic: Microbiology (M)

Infectious diseases are extremely common and every physician needs to be able to correlate clinical findings with the appropriate testing needed. Some infectious disorders will require immediate organism identification, and susceptibility to pharmacotherapy, and understanding principles underlying the different types of microorganisms and their identification is

essential. Many newer techniques have been recently implemented, including molecular techniques, that allow more definitive identification and specialized treatment for infectious organisms.

Learning Goal 1: Pathogenesis, Diagnosis, and Treatment of Infectious Disease

Apply knowledge of infectious organisms to explain the pathogenesis of disease and clinical syndromes, appropriate collection of patient samples, organism identification and classification, antibiotic choice, and selection of medical/surgical interventions.

Objective M1.1: Preanalytic Factors. Explain the types of preanalytical variables that affect diagnostic accuracy and discuss factors that affect length of turn-around time for microbiological workups.

Objective M1.2: Gram Stain. Compare and contrast the interpretations of Gram stains for rapid diagnosis of causative bacterial agents from sterile and contaminated sites and discuss the clinical settings where recognition of bacteria is most meaningful.

Objective M1.3: Identification. Give examples of the types of testing, and their optimal usage, performed in microbiology to identify an infectious disease.

Objective M1.4: Coordination of Treatment. Explain how a process that coordinates identification of the infectious organism, antibiotic sensitivity susceptibility testing, and reporting to the pharmacy antibiotic steward team and treating physician will optimize patient care and reduce health-care costs.

Learning Goal 2: Antimicrobials

Integrate knowledge of antimicrobial agents with bacterial culture and susceptibility testing results to guide treatment of infectious diseases.

Objective M2.1: Mechanisms of Antibiosis. Associate mechanisms of action with antimicrobial agents including the following: disruption of cell wall synthesis, inhibition of protein synthesis, inhibition of DNA synthesis, and antimetabolites.

Objective M2.2: Antimicrobial Activity. State the spectrum of activity for common antimicrobial agents.

Objective M2.3: Antibiotic Resistance. Describe mechanisms of resistance found in common pathogens including the following: Penicillinase and mecA in *Staphylococcus* subspecies, vanA and vanB in *Enterococcus* subspecies, extended spectrum β-lactamases and carbapenemases in *Enterobacteriaceae*.

Objective M2.4: Antimicrobial Susceptibility Testing. Describe the standardized techniques used in antimicrobial susceptibility testing, why standardization is important, and the differences between a qualitative and quantitative result including disk diffusion, broth microdilution, and automated antimicrobial susceptibility testing systems.

Objective M2.5: Genetics of Susceptibility. Name the genetic element detected by extrapolate cefoxitin and oxacillin susceptibility tests and describe how the results for *Staphylococcus* subspecies are used to predict activity of other β-lactam antibiotics.

Objective M2.6: Choice of Antibiotics. Describe how the microbiology laboratory determines if an isolate from a blood culture is susceptible or resistant. Describe how the pharmacokinetic (PK)/pharmacodynamic (PD) models may influence a clinician's choice of antibiotics given the susceptibility of an organism using specific examples.

Objective M2.7: Antimicrobial Stewardship. Outline the principles that guide an institution's reporting cascade for the following: FDA indications, The Clinical and Laboratory Standards Institute (CLSI) guidance, site of infection, institution formulary, and antimicrobial stewardship.

Objective M2.8: Institutional Antibiogram. Use the institutional antibiogram to prescribe therapy before susceptibility test results are available.

Objective M2.9: Molecular Testing in Microbiology. List examples of molecular tests that are commonly used in clinical microbiology, and explain how they have an important impact on clinical care.

Objective M2.10: Mass Spectrometry in Microbiology. Explain how the application of Matrix-assisted Laser Desorption/Ionization-time of Flight (MALDI-TOF) mass spectrometry in the clinical microbiology laboratory can impact patient care.

Objective M2.11: Urine Studies for Cystitis. Explain the role of urine studies, including culture, in selecting antimicrobial therapy for infectious cystitis.

Objective M2.12: Diagnosis of UTI. Describe a testing strategy for a typical uncomplicated community acquired urinary tract infection (UTI) versus a nosocomial UTI in a patient with a Foley catheter and list the key microbiological tests in diagnosis of UTIs.

Objective M2.13: Diagnosis and Management of Syphilis. Explain the role of Venereal Disease Research Laboratory / rapid plasma reagin (VDRL/RPR) and *Treponema*-specific tests in the diagnosis and management of syphilis.

Learning Goal 3: Virology

Integrate concepts of virology with diagnostic techniques including culture, molecular, and antigen diagnostics to identify viral infections and guide treatment.

Objective M3.1: Hepatotropic Viruses. Describe the laboratory findings that diagnose hepatitis and correlate with the different possible clinical outcomes for each of the major hepatotropic viruses.

Objective M3.2: Influenza. Explain the diagnosis of influenza in terms of diagnostic tests used, major antigens present, and the implications of a major shift in these antigens.

Objective M3.3: Serology, PCR, and Culture. Describe the role of serology, Polymerase Chain reaction (PCR), and culture in the diagnosis of viral infections and name which viruses are most rapidly identified by each.

Objective M3.4: HIV Infection. Explain the testing strategy used to diagnose HIV and the role of viral load and CD4 count in monitoring HIV infection.

Objective M3.5: Response to HIV Treatment. Describe the tests available to examine the response of an HIV virus to therapeutic agents, explaining how each test works.

Learning Goal 4: Mycobacteria

Integrate concepts of mycobacteriology with diagnostic techniques including culture, molecular, and antigen diagnostics to identify mycobacterial infections and guide treatment.

Objective M4.1: Identification of Mycobacteria. Describe the diagnostic tests available for the identification of mycobacteria including culture methods and new molecular tests.

Objective M4.2: Antimycobacterial Susceptibility. Compare and contrast the methods, culture, and molecular tests used to identify mycobacteria drug susceptibility and the time required for results by each method.

Learning Goal 5: Mycology

Integrate concepts of mycology with diagnostic techniques including culture, molecular, and antigen diagnostics to identify fungal infections and guide treatment.

Objective M5.1: Types of Fungi and Yeast. Differentiate among filamentous fungi, dimorphic fungi and yeast, and describe the diagnostic approaches for each type.

Objective M5.2: Sensitivity Testing. Define sensitivity testing and describe its role and use in the management of yeast infections.

Objective M5.3: Special Testing for Fungi and Pneumocystis. Explain the basis for the galactomannan and β-glucan tests and how they are utilized to detect fungi and *Pneumocystis*.

Learning Goal 6: Parasitology

Integrate concepts of parasitology with diagnostic techniques including culture, molecular, and antigen diagnostics to identify parasitic infections and guide treatment.

Objective M6.1: Metazoan and Protozoan Parasites. Compare and contrast metazoan and protozoan parasites and the diagnostic approaches to each.

Objective M6.2: Stool Testing for Parasites. Explain the role of stool samples, including number examined, role of microscopy, and coproantigen detection in the diagnosis of parasitic disease.

Objective M6.3: Serologic Testing for Parasites. Summarize the role of serology and serological tests to diagnose toxoplasmosis and assess the risk of transmission during pregnancy.

Objective M6.4: Malaria and Babesiosis. Contrast *Plasmodium falciparum* with other malaria species and babesiosis on a blood smear and explain the role of thick and thin smears in the diagnosis and management of malaria.

Objective M6.5: Rapid Testing for Malaria. Name the rapid tests that do not require blood smears to identify malaria and explain how these tests work.

Topic: Chemistry (CHEM)

Every physician needs to be able to differentiate between multiple different chemical tests in order to confirm a diagnosis or to follow disease progression. An understanding of the major chemical tests, their relationship to pathophysiology of disease progression, and understanding of limitations of such tests is essential for treatment.

Learning Goal 1: Pathogenesis, Diagnosis, and Treatment of Common Disorders

Apply knowledge of biochemistry, pharmacology, and pathogenesis of disease and clinical syndromes to describe the basic cellular and molecular events associated with diseases of specific tissues and organ systems, and the use of laboratory tests to diagnose and manage these diseases including the selection of medical/surgical interventions.

Objective CHEM1.1: Thyroid Disease. Discuss the clinical presentation and the pathophysiologic bases of thyroid diseases including the efficient use of laboratory tests to make a definitive diagnosis and manage the disease.

Objective CHEM1.2: Cardiac Disease. Discuss the clinical presentation and the pathophysiologic bases of cardiac diseases including the efficient use of laboratory tests to make a definitive diagnosis and manage the disease.

Objective CHEM1.3: Endocrine Disease. Discuss the clinical presentation and the pathophysiologic bases of other endocrine diseases including the efficient use of laboratory tests to make a definitive diagnosis and manage the disease.

Objective CHEM1.4: Liver and Gastrointestinal Disease. Discuss the clinical presentation and the pathophysiologic bases of liver and gastrointestinal diseases including the efficient use of laboratory tests to make a definitive diagnosis and manage the disease.

Objective CHEM1.5: Renal Disease. Discuss the clinical presentation and the pathophysiologic bases of renal diseases including

the efficient use of laboratory tests to make a definitive diagnosis and manage the disease.

Objective CHEM1.6: Lung Disease. Discuss the clinical presentation and the pathophysiologic bases of lung diseases including the efficient use of laboratory tests to make a definitive diagnosis and manage the disease.

Objective CHEM1.7: Toxicology. Determine the value of testing for drugs and toxins accounting for the routes of administration, distribution and metabolism of the agent of interest, including the specimen source, the analytes to be detected given the medical questions, and the timing constraints for specimen collection.

Objective CHEM1.8: Cancer Diagnostics. Select and interpret appropriate tests for specific cancer diagnostics, including tumor markers and serum monoclonal protein analysis.

Topic: Immunology (IMM)

Every physician needs an understanding of specific laboratory tests to differentiate between inflammatory and immune-mediated diseases. Many newer techniques have been recently implemented that allow more definitive diagnosis and specialized treatment for these disorders.

Learning Goal 1: Pathogenesis, Diagnosis, and Treatment of Immunologic Disorders

Apply knowledge of immunology, biochemistry, and pathology to describe the basic cellular and molecular events associated with immune system diseases of specific tissues and organ systems and the use of laboratory tests to diagnose and manage these diseases.

Objective IMM1.1: Markers of Inflammations. Compare and contrast markers of inflammation in terms of the pathophysiologic basis and stages of the inflammatory response.

Objective IMM1.2: Autoimmune, Immune Deficiencies, and Allergen Testing. Select and interpret appropriate tests for workup and interpretation of autoimmune disease, immunodeficiencies, and allergy testing.

Objective IMM1.3: Serologic Testing for Infection. Discuss, with examples, the application of serological testing in infectious diseases to establish immune status and diagnose infection.

Objective IMM1.4: Autoimmune Diseases. Discuss the clinical presentation and pathophysiologic bases of autoimmune diseases including the efficient use of laboratory tests to make a definitive diagnosis and manage the disease.

Topic: Genomics (GE)

Every physician needs an appreciation of the complex field of genomics including Mendelian inheritance patterns to the ever evolving molecular techniques that are essential for diagnosing diseases as accurately as possible, and for many diseases correlated with specific targeted immune or chemotherapy to maximize effectiveness of treatment, decrease side effects, and optimize patient survival.

Learning Goal 1: Genes

Apply knowledge of genetics including the structure and organization of the human genome and regulation of gene expression, genetic variation, and inheritance patterns to basic disease processes.

Objective GE1.1: Mendelian Inheritance. Describe molecular testing of Mendelian inheritance including autosomal dominant, autosomal recessive, X-linked; non-Mendelian inheritance including mitochondrial and imprinting; unstable repeat expansions; and cytogenetic translocations.

Objective GE1.2: Pedigrees and Mutations. Demonstrate how to take a 3-generation family history and draw a pedigree. Distinguish between a nonpathogenic polymorphism and a pathogenic mutation, and describe the mechanisms that produce different types of mutations.

Objective GE1.3: Inheritance Patterns. Compare diagnostic testing of single-gene disorders to diseases with complex inheritance patterns and include the role of rare, high-risk variants, and common, low-risk variants.

Objective GE1.4: Linkage Analysis. Outline the principles that underlie genetic linkage analysis and association studies and how they are used to identify genes associated with diseases.

Objective GE1.5: Population Genetics. Define the concepts "founder effect" and "genetic drift" and explain how genetic variants are distributed within populations.

Objective GE1.6: Genetic Risk. Explain how genetic risk is determined by carrier status and carrier frequency of a condition and determine carrier frequencies and incidence of recessive conditions using Hardy-Weinberg Laws.

Objective GE1.7: Phenotypic Expression. Distinguish dominant and recessive phenotypes and alleles and describe how incomplete penetrance, variable expressivity, imprinting, and pleiotropy affect the phenotypic expression of diseases.

Objective GE1.8: Modifier Genes. Describe the concept of a modifier gene and its contribution to phenotypic variability.

Objective GE1.9: Cytogenetics. Define the following cytogenetic terms and nomenclature: karyotype, euploidy, aneuploidy, monosomy, trisomy, deletion, ring chromosome, inversion, isochromosome, translocation, balanced reciprocal translocation, Robertsonian translocation.

Objective GE1.10: Mosaicism. Define mosaicism and explain how it affects the phenotype of a chromosomal disorder.

Learning Goal 2: Chromosomal Disorders

Apply knowledge of genetics to explain the molecular basis of single-gene and nonneoplastic chromosomal disorders.

Objective GE2.1: Testing for Genetic Disorders. Describe the genetic and epigenetic causes, pathophysiology and clinical manifestations, and optimal laboratory tests used to diagnose the following specific genetic disorders: Mendelian, autosomal disorders (dominant and recessive), X-linked disorders, chromosomal disorders, and disorders of nonclassic inheritance.

Learning Goal 3: Genetic Basis of Neoplasia

Apply knowledge of genetics to explain the genetic basis for neoplasia, and the role of genetic testing in diagnosis and treatment of diseases.

Objective GE3.1: Genetic Redisposition to Neoplasia. Describe 3 mechanisms by which genes predispose to neoplasia: oncogenes, tumor suppressor genes, DNA repair genes.

Objective GE3.2: Genetic Mechanisms of Neoplasia. Describe the molecular genetic mechanisms that underlie cancers: germline mutations; somatic mutations including point mutations, deletions, amplifications and translocations; epigenetic changes.

Objective GE3.3: Molecular Testing in Oncology. Explain the application of molecular testing for diagnosis, prognostication, and therapeutic follow-up of oncologic diseases.

Learning Goal 4: Reproductive Genetics

Apply knowledge of genetics to explain the role of reproductive genetics and population screening.

Objective GE4.1: Carrier Testing. Describe the role of preconception and prenatal carrier testing for genetic disorders depending upon family history and ethnic background.

Objective GE4.2: Newborn Screening. Describe the rationale for newborn screening for genetic diseases and explain the difference between screening and diagnostic testing.

Learning Goal 5: Diagnosis, Treatment, and Counseling

Apply knowledge of genetics to explain the role of genetic testing in diagnosis and treatment of diseases and in counseling of patients and families.

Objective GE5.1: Treatment Mechanisms. Explain the mechanisms involved in the treatment of genetic diseases: organ transplantation, manipulating metabolic pathways, correction of defective structural proteins or enzymes, modulation of RNA expression, alteration of DNA sequence, and alteration of gene expression.

Objective GE5.2: Genetic Variation in Response to Treatment. Describe how genetic variation can predict response to medications, dosing, and risk for adverse effects.

Objective GE5.3: Factors to Prevent Disease in the Genetically Predisposed. Describe how modification of nongenetic factors can prevent or mitigate disease in genetically predisposed individuals.

Objective GE5.4: Genetic Counseling. Describe the role of genetic counselors in patient care and when to make appropriate referrals for genetics evaluations.

Topic: Autopsy (AU)

Autopsy is a division of anatomic pathology that encompasses the examination of a deceased person, either for medical or legal reasons. Understanding the value of the autopsy, both for scientific investigation of potential inherited disorders and for understanding the diseases that led to a patient's demise will allow clinicians appropriately discuss this end-of-life medical evaluation.

Learning Goal 1: Value of the Autopsy and Obtaining Consent

Apply knowledge of clinical medicine and quality management to discuss the value of the autopsy and procedures for obtaining permission for postmortem examination.

Objective AU1.1: Value of the Autopsy. Provide examples demonstrating the value of the autopsy toward improvement in clinical diagnosis and management, quality control, medical education, research, and elucidation of "new" diseases.

Objective AU1.2: Consent for Autopsy. Identify the legal next of kin or individual authorized to consent when obtaining consent for an autopsy.

Objective AU1.3: Obtaining Consent from the Family. Describe how to approach a family to request consent for an autopsy, including a discussion of the autopsy procedure in language that the patient's family can understand.

Objective AU1.4: Professionalism in the Autopsy. Discuss the psychosocial–emotional aspects of the autopsy experience, including its role in closure, and the importance of communication and professionalism among the health-care team.

Learning Goal 2: Death Certificate

Apply knowledge of quality management to discuss the utility of death certificates and proper approaches for completing them.

Objective AU2.1: Public Health. Describe the importance of death certificates for tracking and analysis of public health trends.

Objective AU2.2: Components of the Death Certificate. Discuss the key components of the death certificate; differences among immediate, intermediate, and underlying (proximate) cause of death based on disease process; and the role of mechanisms of death on a death certificate.

Objective AU2.3: Medical Errors. Explain how under- or overutilization of medical care, and incorrect diagnoses, therapeutics, or informed consent can lead to medical errors and give examples of how an autopsy can identify errors thereby improving health care and decision-making.

Learning Goal 3: Forensic Autopsy

Apply knowledge of clinical medicine and postmortem examination to discuss the indications for medical examiner referral and special procedures in the forensic postmortem examination.

Objective AU3.1: Role of the Medical Examiner. Define the role of a medical examiner in terms of public health and protection of legal rights.

Objective AU3.2: Reportable Deaths. Identify circumstances of death that need to be reported to the medical examiner/coroner.

Topic: Surgical Pathology (SP)

Surgical pathology is the area of anatomic pathology where all tissues or hardware removed from a patient is evaluated. Specimens sent to surgical pathology may range from minute endoscopic biopsies to large organ resections. Special techniques are commonly used by pathologists in evaluating these specimens that allow for definitive diagnosis and the recommendation of appropriate treatment for both benign and malignant lesions.

Learning Goal 1: Role in Diagnosis

Apply knowledge of clinical medicine and pathology to describe the roles cytology and surgical pathology play in diagnosis and treatment of benign and malignant disorders. Use specific examples from the most common diseases and forms of cancer.

Objective SP1.1: Obtaining the Specimen. Describe the procedures for obtaining a biopsy of a tissue lesion or mass in different sites, including superficial and deep soft tissues, solid organs, and tubular organs. Associate each procedure and specimen type to either cytology or surgical pathology and give examples of possible reasons and follow-up for false negative biopsies.

Objective SP1.2: Differential Diagnosis. List the major differential diagnoses for each type of cytology or surgical pathology specimen derived from a lesion or mass and describe appropriate further studies, both special stains and immunohistochemistry.

Objective SP1.3: Special Studies. After looking at slides of a tissue lesion or mass, the pathologist makes a diagnosis. List options for surgical and nonsurgical treatment and describe prognostic and therapy-guiding tests that may be performed on the tissue.

Objective SP1.4: Staging. Describe the information that the pathologist obtains from a resected tissue specimen, how this information is reported, how it is combined with clinical information to stage the tumor, and how staging information is used to guide treatment.

Learning Goal 2: Immune and Infectious Diseases

Apply knowledge of clinical medicine and pathology to describe the roles cytology and surgical pathology play in diagnosis and treatment of inflammatory disease, in particular those with immune or infectious etiologies.

Objective SP2.1: Examples of Inflammatory Conditions. Give examples of specific sites and diseases in which specific pathologic diagnoses of inflammatory and/or infectious conditions are critical to treatment and prognosis.

Learning Goal 3: Congenital Disorders

Apply knowledge of clinical medicine and pathology to describe hereditary/malformative disorders, in terms of clinically useful information that anatomic pathology diagnosis can provide.

Objective SP3.1: Terminology. Define general terminology for pathologic features that are associated with hereditary/malformative disorders.

Learning Goal 4: Interpretation of Reports

Apply knowledge of clinical medicine and communication skills to interpret pathology reports and communicate the results to patients in the context of risk assessment and patient prognosis. Determine appropriate action including additional testing and clinical evaluation.

Objective SP4.1: Explaining the Report to the Patient. Explain the results of a pathology report to a patient in language the patient can understand.

Learning Goal 5: Classification of Leukemia and Lymphomas

Apply knowledge of pathology and the application of diagnostic decision trees to discuss the classification systems of leukemia and lymphomas, and describe the relative roles of ancillary laboratory studies in classification.

Objective SP5.1: Special Studies. Describe the roles of immunohistochemistry, flow cytometry, cytogenetics, and molecular diagnostics in the diagnosis and classification of lymphoma, and explain how, with examples, different techniques are most appropriate in diagnosis, staging, and management of disease.

Objective SP5.2: Use of Special Studies. Explain how the work up of lymph nodes at the frozen section bench differs from routine frozen sections, and how examination of touch preparations of slides are used to streamline use of additional special techniques.

Objective SP5.3: Differential Diagnosis. Discuss how a pathologist can use a diagnostic decision tree to make a diagnosis

efficiently, minimize the time to report results to the oncologist, and optimize treatment decisions.

Topic: Cytopathology (CYP)

Cytopathology focuses on the individual cellular components of disease. Cytopathological examination is an essential tool for its wide-ranging reach in screening, diagnostics, prognostics, and prevention of advanced disease states. Furthermore, the minimally and noninvasive nature of ascertaining most cytological specimens allows for immediate access to viable cellular material for advanced testing, molecular, and biochemical analyses.

Learning Goal 1: Cytologic Diagnosis

Apply knowledge of general and systems pathology to understand the meaning and context of cytologic diagnoses.

Objective CYP1.1: Obtaining the Specimen. Compare and contrast the 3 basic methods to obtain cytologic material for diagnosis, describe the settings in which these can be used to diagnose benign and malignant conditions, and discuss the limitations of each.

Objective CYP1.2: Categorizing Diagnostic Certainty. Compare and contrast the degree of diagnostic certainty applied to general categorization in cytologic diagnosis.

Objective CYP1.3: Identifying Infectious Diseases. Describe the uses and limitations of cytology, with examples, in identifying common infectious diseases.

Objective CYP1.4: Use of Cytology for Staging of Neoplasms. Describe how cytologic specimens can add valuable information for tumor staging.

Learning Goal 2: Advantages of Cytopathology

Apply knowledge of clinical medicine, pathology, and healthcare delivery to describe the advantages cytopathologic examination offers over conventional pathologic tissue examination.

Objective CYP2.1: Screening. Describe the principles of an effective screening test and the uses and limitations of cytology.

Objective CYP2.2: Adjunct Testing (HPV). Describe how adjunct testing is used in conjunction with cytology examination.

Objective CYP2.3: Cervical Screening. Describe how to find and utilize current algorithms for management of cervical screening.

Authors' Note

The opinions expressed are those of the authors and do not reflect the official positions of the Uniformed Services University, the US Army, Navy, Air Force, or DoD.

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Competency 1: Disease Mechanisms and Processes

Educational Case Background & Submission Instructions

Background

Becoming a competent physician requires the ability to gain a broad foundation of knowledge, skills, and attitudes essential for independent medical practice. Essential in this is the understanding of the normal and pathological processes of each organ system, the ability to apply disease mechanisms to describe the pathobiology, and the ability to continually improve the diagnostic acumen and optimal treatment decisions through lifelong learning.

The Pathology Competencies for Medical Education (PCME) have detailed learning objectives under each goal that direct medical students and course directors to important facets of each learning goal that can be individually applied by learners. The competencies are divided into three sections—disease mechanisms and processes, organ system pathology, and diagnostic medicine and therapeutic pathology—and allow flexibility for each medical school and learner to apply the learning goals and objectives in a way that can keep the unique design of each curriculum or learning plan. The competencies are purposefully kept broad as they represent the minimum requirements of what pathology course directors across the nation have agreed upon to prepare medical students for entry into any residency program and for the subsequent contemporary practice of medicine.

Educational Cases for the PCME are current, peer-reviewed, and highlight the pathology competencies through fictional (but realistic) learning cases that can easily be adapted to multiple types of educational modalities. Educational Cases reference at least one primary learning objective, but may have one or more secondary learning objective(s). The pathology competencies and learning objectives are clearly indicated in the beginning of each case so that the focus of the educational case is evident. Key elements of the current format include clinical presentation, discussion questions or points, learning points, and references. The clinical presentation may include images or laboratory data for the patient's presentation. The discussion questions or points are questions or statements that promote clinical reasoning followed by detailed explanations of the pathology, medicine, or therapeutics brought up in the discussion point or question. The learning points at the end of the case highlight the main teaching points from the preceding discussion. Thus, the cases demonstrate the application of medical reasoning to clinical scenarios that allow the learner to understand and apply diagnostic principles, incorporating morphologic findings and laboratory values with discussion of the laboratory medicine essentials for accurate diagnosis and treatment. References are included in each case and will allow the reader to review the original sources used to create the learning case or gain additional in-depth information. Thus, the Educational Cases are written in a style that can be easily used or adapted to multiple educational formats, such as small group discussions or flipped classrooms.

Case Submission Guidelines

- Submission Portal: https://mc.manuscriptcentral.com/apc
- Manuscript Type: *Educational Case*
- Key Words:
  - *list "pathology competencies" as first keyword*
  - *list relevant competency, topic, learning goal, and objective keywords, e.g. "disease mechanisms, genetic mechanisms, inheritance patterns"*
  - *other relevant keywords from the case content, e.g. "cystic fibrosis"*
- Abstract: *"None needed"*
- Case Content:
  - Primary (and secondary if applicable) learning objective(s), cited from the PCME (doi: 10.1177/2374289517715040)
    - Example of primary objective formatting:
      Objective GM1.2: Inheritance Patterns. Compare and contrast the inheritance patterns of different types of Mendelian disorders and give examples of each type of pattern.
      Competency 1: Disease Mechanisms and Processes; Topic GM: Genetic Mechanisms; Learning Goal 1: Genetic Mechanisms of Developmental and Functional Abnormalities.
  - Patient Presentation: *Include presentation (History of present illness, past medical history, etc. and physical examination)*
  - Diagnostic Findings: *This can include laboratory findings or histology.*
  - Questions/Discussion Points: *The questions and discussion points should be presented in a logical order to promote clinical reasoning. In addition, you can include additional laboratory data/histologic images in later discussion points. The discussions should thoroughly explain the learning objectives to which the case is applied.*
  - Teaching Points: *These should be covered in your discussion.*
  - References: *Linked to the discussion.*
- Images (if applicable): *All images must be original work or have appropriate approval for publication.*

Accepted Cases

Published Educational Cases receive the same scholarly recognition, citation and merit as other articles published in *Academic Pathology*. Cases accepted for publication will incur an Open Access article processing fee of $500.00 for authors who are faculty and students of APC member departments; $750 for non-members. For more information, contact *Academic Pathology* at journal@apcprods.org or 302-660-4940.

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Educational Case: Cervical Neoplasia: HPV and Its Link to Cancer

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, disease mechanisms, HPV, human papillomavirus, cervical cancer, neoplasia, disease screening, PAP smear

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Primary Objective

Objective N3.1: Morphologic Features of Neoplasia: Describe the essential morphologic features of neoplasms and indicate how these can be used to diagnose, classify, and predict biological behavior of cancers.

Competency 1: Disease Mechanisms and Processes; Topic N: Neoplasia; Learning Goal 3: Characteristics of Neoplasia.

Secondary Objectives

Objective CYP2.1 Screening: Describe the principles of an effective screening test and the uses and limitations of cytology.

Objective CYP2.2 Adjunct testing (HPV): Describe how adjunct testing is used in conjunction with cytology examination.

Objective CYP2.3 Cervical Screening: Describe how to find and utilize current algorithms for management of cervical screening.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic CYP: Cytopathology; Learning Goal 2: Advantages of Cytopathology.

Patient Presentation

A 45-year-old female presents to her new primary care physician to establish care after not visiting a doctor for 10 years. She was recently referred for a follow-up visit after receiving an abnormal liquid Pap result from a free community outreach cervical cancer screening program. She denies any significant past medical or surgical history. The patient's last menstrual period was 2 weeks ago, and she is currently sexually active with multiple partners. She occasionally uses barrier methods of contraception. Physical examination and pelvic examination are within normal limits. Before discussing the results, the patient remembers having a history of abnormal pap smears that required further testing, but these were not pursued since she was lost to follow-up.

Diagnostic Findings

Upon further review of the patient's history, the patient was 35 years old at the time of her last Pap test and pelvic examination. Cytology of her old Pap test showed a low-grade squamous intraepithelial lesion (LSIL). Human papillomavirus

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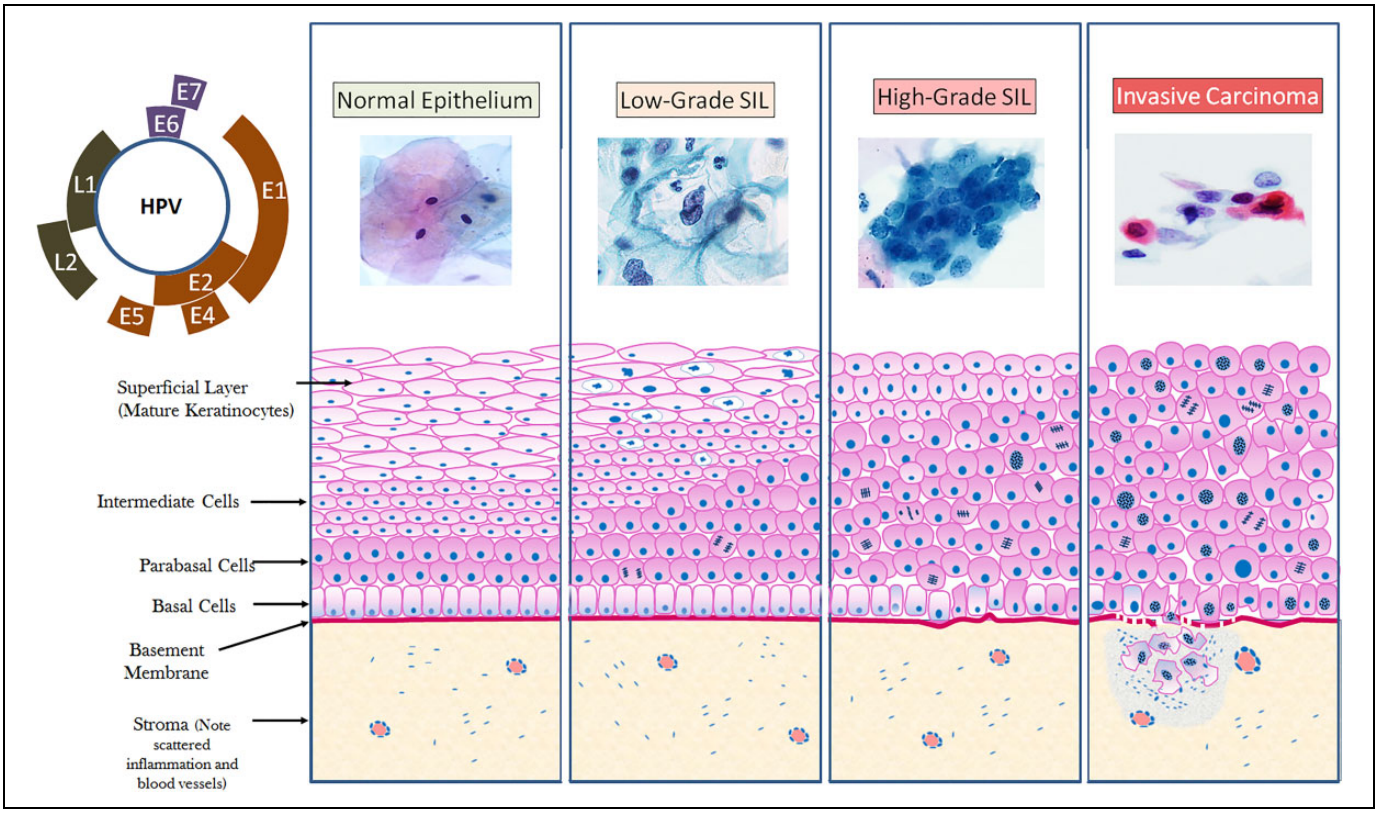

Figure 1. Sketch demonstrating the progressive nature of the dysplastic changes leading to the development of cancer. To the left is a representation of the HPV genome with its associated early and late antigen proteins. HPV indicates human papillomavirus.

(HPV) co-testing results from that time demonstrated positivity for HPV type 16. As per American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines, the patient was recommended to undergo further testing with colposcopy but was lost to follow-up.

The patient's current cytologic evaluation is consistent with high-grade squamous intraepithelial lesion (HSIL), and HPV testing remains positive for HPV type 16. Gonorrhea/chlamydia testing is negative. The patient is now scheduled for an immediate colposcopy and loop electrosurgical excision (LEEP).

Questions/Discussion Points

What Are Your Preliminary Working Diagnosis and Its Differential?

This patient cytology results previously demonstrated an LSIL, which has since progressed to an HSIL with persistent HPV infection. The SILs are virally driven neoplastic proliferations of cervical epithelial cells and are precancerous. Epidemiological studies have demonstrated the time-dependent progressive nature of these lesions (Figure 1). The differential diagnosis may include other types of cervical lesions, such as squamous metaplasia, reactive changes, or glandular changes. Invasive squamous cell carcinoma of the cervix (when a precancerous lesion invades beyond the basement membrane) should not be ruled out and is the primary concern for this patient.

What Screening Modalities Are Recommended to Detect Cervical Lesions and How Do They Impact Disease Progression?

Cervical cytologic screening was introduced decades ago and is still the most effective cancer prevention test today. For example, cytology screening that is only performed twice in a woman's life can reduce her risk for cervical cancer by 43%.[1] Cytologic testing and HPV co-testing for HPV infection decrease the prevalence and mortality of cervical cancer. Furthermore, regular screening allows for early intervention and reduces progression of disease.

Since cervical SIL is mostly a disease of reproductive-aged women, the American College of Obstetricians and Gynecologists (ACOG) recommends women aged 21 to 29 years have a Pap test every 3 years without HPV testing. Women aged 30 to 65 years should have a Pap test and co-testing for HPV every 5 years.[2]

HPV testing is not recommended for women younger than 30 years because the prevalence of HPV positivity is very high in these women, and the vast majority will completely clear their infections within 1 year.[3] However, for women older than 30 years, liquid-based Pap screening in conjunction with HPV co-testing has a lower false-negative rate and will detect a greater number of patients at risk compared to Pap testing alone.

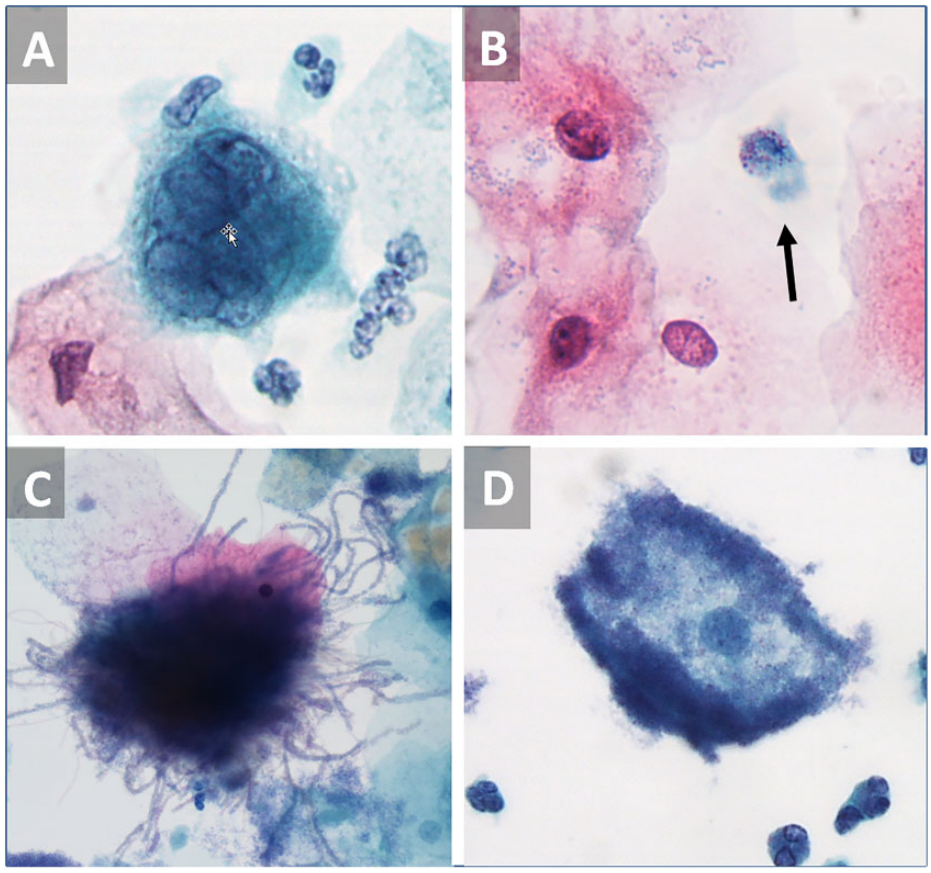

Figure 2. Common infectious findings on Pap smear: (A) herpes simplex virus, (B) trichomonas vaginalis (arrow pointing to trichomonal parasite), (C) actinomyces, (D) Clue cell (indicating a shift in vaginal flora).

In 2014, the ATHENA (Addressing THE Need for Advanced HPV diagnostics) study examined the ability of HPV testing alone to identify women at risk of developing cervical squamous lesions. The study demonstrated that primary screening using only HPV testing can be an effective screening strategy in some patients. Based on data from this study, the Food and Drug Administration (FDA) approved the use of 1 HPV test (Roche Cobas HPV test) for primary cervical cancer screening (without cytology) in women aged 25 years and older.

Although HPV testing may be able to identify the presence of nucleic acids from high-risk HPV types and serial testing can demonstrate persistent infection, Pap testing still has several advantages over HPV testing alone. Since the Pap smear is not designed solely around HPV, it can provide tremendous additional information about the cervical and sexual health of a woman. Although not initially designed for this purpose, the Pap smear can identify numerous infections, including herpes, trichomonas, actinomyces, and bacterial vaginosis (Figure 2). It can even identify the presence of cancer cells from other gynecological sites, such as endometrial carcinoma. Additionally, Pap staining, which is designed to identify the lesions produced by HPV infections, can provide information about how progressive the disease has become whereas HPV testing alone cannot.

Why Is Cervical Cancer, in Particular, a Disease for Which It Is Appropriate to Create a Screening Program?

In 1968, James Wilson published a World Health Organization pamphlet that addressed objective principles which any successful screening program must meet.[4] The principals were primarily not only related to the disease itself but also addressed case identification through testing. In brief, Wilson established that in order for a screening program to be successful, the associated disease must be a public health burden, there should be a pathophysiologic understanding of the disease, there must be a predisease state in which we can identify possible cases, there should be a cost-effective test for the disease and there should be an available treatment for the disease. Cervical cancer, along with our understanding of HPV-related neoplasia and progression to cancer, successfully meets all of these requirements and, therefore, was historically a prime candidate for a screening strategy.[4]

Explain the Pathophysiologic Process That Occurs in the Development of Squamous Intraepithelial Lesion/Cancer: How Is Human Papillomavirus Involved?

The HPV genotypes which have a documented association with squamous lesions and can progress to invasive cancer are termed "high risk." Other "low-risk" genotypes may cause other lesions such as genital warts but do not progress to cancer. Of the high-risk HPV types, genotypes 16 and/or 18 have been identified in the majority of cervical cancers.

The pathogenesis of cervical cancer requires 2 biologically interrelated features: a productive HPV viral infection and an epithelial neoplastic process. According to this model, there is initially an infection with a high-risk type of HPV that persists and progresses to a pathologically defined precursor lesion and ultimately to invasion[3] (Figure 1).

Squamous lesions develop after HPV infected the basal or primitive cells of the immature squamous epithelium through defects or breaks in the skin or mucous membranes. The early region of the HPV genome includes transforming regions E6 and E7 whose corresponding proteins bind to and inhibit the host cell–regulatory proteins, p53 and Rb. This causes unrestricted cell proliferation and blocks cellular apoptosis. Most SIL starts at the squamocolumnar junction of the transformation zone of the cervix. Viral DNA replication occurs mostly in the superficial and intermediate cell layers of the squamous epithelium. As these infected cells move to the epithelial surface, differentiation-specific transcriptional factors from the host cells stimulate the production of viral capsid proteins and subsequently intact virions that produce characteristic cytologic and histologic changes[3] (see Figure 1).

Describe the Natural History of Human Papillomavirus Infections and Its Relation to Neoplasia

Most HPV infections are transient, becoming latent or undergoing immunologic clearance within 1 to 2 years of diagnosis.[1] However, infections with high-risk types of HPV clear more slowly and persistence of infection increases the likelihood of developing high-grade lesions. Prevalence of HPV infection peaks in the late teens to early 20s, while the incidence of cervical cancer in unscreened populations ranges from 35 to 55 years of age. Since HSIL is more common than invasive cervical cancer, this suggests that only a small portion of HSIL progresses to malignancy.[1] We, therefore, understand that although the development of invasive cervical cancer requires persistent infection with high-risk types of HPV, it is not always sufficient to cause cancer. Other associated risk factors include cigarette smoking, long-term use of combined oral contraceptive pills, and immunosuppression.[3]

Describe the Cytopathological Features of Some Common Cervical Infections Which Can be Found on the Pap Stain

Cervical cytology has relatively high specificity for most organisms and can help guide clinical management (see Figure 2).

A. Herpes simplex virus (HSV): The classic features of HSV infections on Pap staining are described as the "three M's of herpes": multinucleation, margination of chromatin, whereby the rim of the individual nuclei appears darker staining than the center, and molding which is seen as each nucleus indenting the neighboring nuclei. With the accumulation of viral particles, the nuclei may develop a "ground glass" appearance.
B. Trichomonas vaginalis: The parasitic organisms are visible with liquid-based preparations. They appear as pear-shaped organisms with an eccentrically located nucleus, eosinophilic cytoplasmic granules, and flagella.
C. Actinomyces: Clumps of woolly filamentous organisms which are usually deeply staining and may demonstrate acute angle branching.
D. Clue cells: Irregularly shaped squamous cells covered with darkly staining coccobacilli. These cells typically indicate a change in the cervical microbiological flora and may be an indication of bacterial vaginosis.

What Systems Are Used to Classify Lesions Identified by Cervical Cytology? How About Classification of Cervical Histopathology?

The Bethesda System (TBS) is used to categorize cytological diagnoses, while the Lower Anogenital Squamous Terminology (LAST) project describes histological findings associated with HPV throughout the anogenital tissues, including the cervix.[5] The Bethesda system utilizes a 2-tiered system of classification (LSIL or HSIL) and previously histopathologists utilized a 3-tiered system (cervical intraepithelial neoplasia [CIN]-I, CIN-II, and CIN-III). Large studies have demonstrated significant diagnostic variation between CIN-II and CIN-III; additionally, CIN-II lesions were found to demonstrate similar rates of progression of disease to CIN-III in some instances. For these reasons, the LAST project has adopted a 2-tiered diagnostic system and both LAST and TBS are in line with one another.[6]

Compare and Contrast Cytopathology and Histopathology in the Images

A. Cytology LSIL:

Cells have enlarged nuclei, about 4 times the size of a normal intermediate cell nucleus. The nuclei are darker (hyperchromatic) with wrinkled irregular nuclear membrane contours. Cells may be multinucleated as seen in the image and the chromatin is finely granular. Areas of clearing around the nucleus (koilocytosis), a hallmark of LSIL, are also seen (Figure 3).

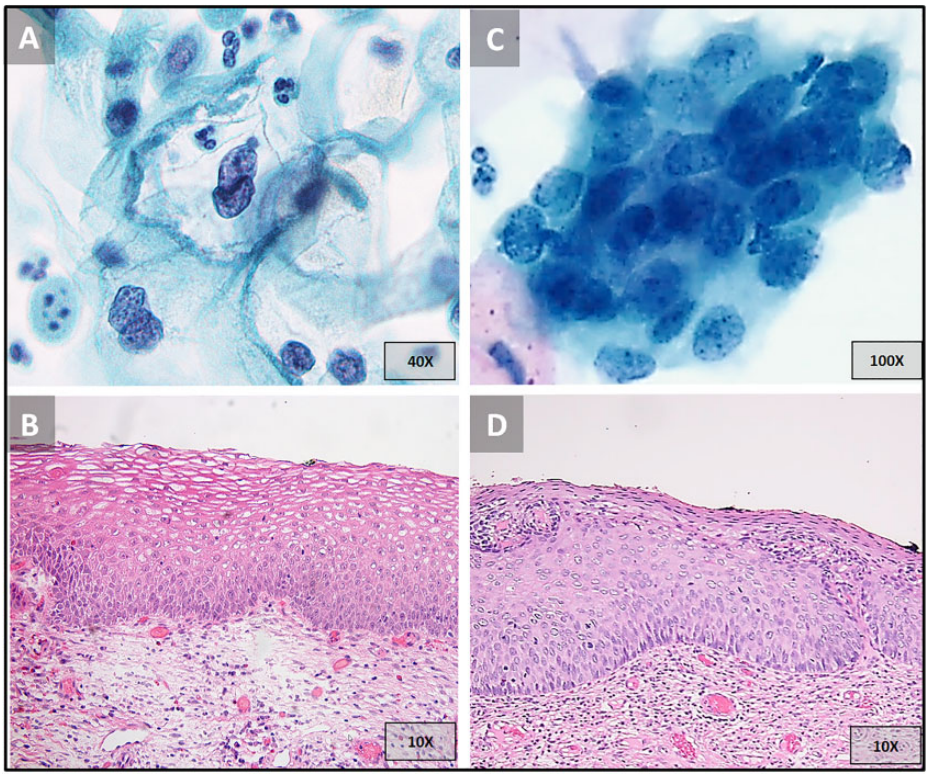

Figure 3. Cytologic and histologic images of low-grade SIL (A, B) and high-grade SIL (C, D). SIL indicates squamous intraepithelial lesion.

B. Histology LSIL (Previously CIN-I):

Nuclei are enlarged and irregularity shaped. There is also darkening of the chromatin (hyperchromasia). Koilocytes with their large vacuoles can be seen in the middle layers, while the superficial layers still resemble a fairly normal basket weave appearance of unaffected epithelium. Overall, there is increased thickness of the epithelium.

C. Cytology HSIL:

The degree of nuclear atypia is increased, such that the nuclei of these cells appear more hyperchromatic and irregular. The amount of cytoplasm decreases as nuclear to cytoplasmic (N:C) ratio increases. The classical features of a mature squamous cell with abundant cytoplasm are no longer seen, and these cells appear less differentiated.

D. Histology HSIL:

Undifferentiated neoplastic cells which no longer resemble the normal squamous cells are present in all layers of the epithelium. The lower layers of the epithelium (basal and parabasal) are thickened, and abnormal mitotic figures are visible. There is nuclear crowding, and cellular variation (pleomorphism) is seen. These areas may appear "bluer" under the microscope because there is less pink cytoplasm. The N:C ratio is high due to scant cytoplasm.

What Is the Recommended Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors? How Should You Proceed Now With More Advanced Disease Present?

The ASCCP *Updated consensus guidelines for managing abnormal cervical cancer screening tests and cancer precursors* outlines the recommendations for managing patients with cervical cytological abnormalities. Although it takes many years for HSIL to progress to invasive cancer, untreated higher grade lesions are also more likely to persist and progress than regress.[3] Therefore, appropriate disease follow-up and management are crucial.

Since our patient now presents with evidence of HSIL on cytology, it is recommended that she undergoes an immediate LEEP or colposcopy with endocervical assessment. Management by ASCCP guidelines differs depending on the colposcopy results. If the biopsy confirms HSIL, either excision or ablation of the "transformation zone" is recommended, followed by co-testing at 12 and 24 months.[1]

What Other Factors Aside From Screening May Alter the Future Burden of This Disease on the Population?

The HPV is an immunologically cleared infection. As such, it was a prime candidate for the development of a multivalent HPV vaccine. Currently, there are 3 FDA–approved HPV vaccines on the

market: Gardasil, Gardasil 9, and Cervarix. The Cervarix vaccine is designed for immunity against HPV 16 and HPV 18, the 2 most common high-risk HPV types that cause about 70% of cervical cancer. Gardasil adds coverage for 2 additional low-risk HPV genotypes (6 and 11) which are the major cause of genital warts. Gardasil 9 extends coverage further to 5 additional high-risk HPV genotypes associated with cervical cancer. These vaccines consist of nonreplicative viral-like particles which provoke an immune response and provide humoral immunologic memory.[7] Currently, several international health-based organizations recommend HPV vaccination be a part of all routine immunization programs. It is important to note that screening following immunization is still required and we have discussed several additional benefits to screening beyond identification of HPV infection.

Describe Some Possible Therapies That Are Being Developed to Treat Human Papillomavirus–Associated Lesions and Cancers

While the initial therapy of squamous lesions is currently complete excision, other novel therapies are currently being evaluated. We have discussed vaccines to prevent infection that are widely available and utilize viral structural proteins. There are currently in development vaccines that help a person's immune system to clear the HPV after infection. Most of these vaccines target HPV oncoproteins E6 and E7.[8] This treatment is anticipated to become clinically available in the near future to decrease the HPV-associated disease burden. Furthermore, research on a pelvic sentinel lymph node biopsy procedure, immunotherapy, and targeted drug therapy is also being conducted.

Teaching Points

- Characteristic cytologic and histologic features, such as koilocytosis, enlarged nuclei, and increased N:C ratio, allow pathologists to diagnose and classify different grades of squamous cervical pathology from low-grade to high-grade squamous lesions and ultimately to carcinoma.
- Classifications based on these features allow one to predict the biologic behavior and malignant potential of these precancerous lesions.
- HPV infection, particularly with high-risk types of HPV, is not only a major risk factor for developing cervical SIL/cancer but also a crucial factor in the pathogenesis of this disease.
- Adequate screening for cervical precancerous pathology may include both cytology Pap and ancillary HPV testing as each method has distinct advantages for the detection of pathologic conditions.
- Cervical disease and its associated diagnostic testing are a paradigmatic model of disease screening and intervention and remain one of the most successful screening programs ever devised.
- Several organizations, including the ACOG and the ASCCP, regularly publish guidelines related to screening and management of the cervical cancer.

Declaration of Conflicting Interests

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Educational Case: A Uterine Neoplasm: Leiomyoma—A Benign Neoplasm

Margret S. Magid, MD[1]

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, disease mechanisms, neoplasia, anaplasia, benign, hyperchromatic, hysterectomy, invasion, leiomyoma, leiomyosarcoma, malignant, metastasis, myomectomy, myometrium, normochromatic, nuclear:cytoplasmic ratio, paraneoplastic syndrome, pleomorphic, poorly differentiated, smooth muscle tumor, well-differentiated

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Primary Objective

Objective N3.1: Morphologic Features of Neoplasia. Describe the essential morphologic features of neoplasms and indicate how these can be used to diagnose, classify, and predict biological behavior of cancers.

Competency 1: Disease Mechanisms and Processes; Topic N: Neoplasia; Learning Goal 3: Characteristics of Neoplasia.

Patient Presentation

A 39-year-old P3013 woman presented to her gynecologist with complaints of increased bleeding during menstruation, back pain, and a feeling of rectal fullness. Pregnancy test was negative. Her gynecologist palpated a large irregular, asymmetric uterus. The patient underwent hysterectomy.

Diagnostic Findings

Examination of the hysterectomy specimen in surgical pathology showed it to be enlarged and distorted by multiple tumors within the myometrium. Figure 1 is a cross section through the uterus and the largest tumor.

Questions/Discussion Points

In Figure 1, describe the cut surface of the tumor.

The cut surface is homogeneously white. There are no areas of grossly recognizable necrosis or hemorrhage, which may be indicative of more aggressive tumors.

In Figures 1 and 2, how would you describe the border of the tumor nodule with the surrounding uterus?

Figure 2 is a low-power photomicrograph from the specimen.

The borders are smooth and "pushing" (not infiltrating into the surrounding myometrium).

What information does this give you about the nature of the tumor?

This gross feature favors that the tumor is benign.

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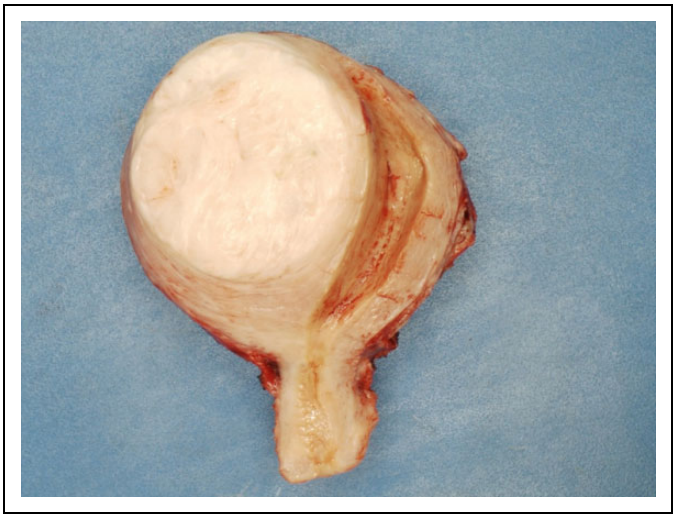

Figure 1. Gross image of the hysterectomy specimen. The cervix is at the bottom of the image. The intramural tumor on the left is compressing the endometrial cavity toward the right.

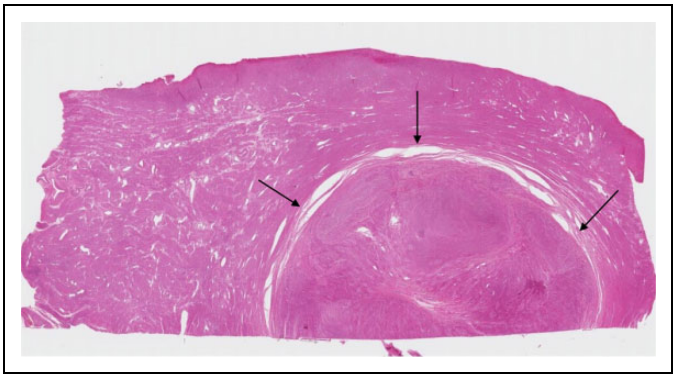

Figure 2. Histological section from the hysterectomy specimen, taken from the intersection of one of the nodules and the adjacent myometrium. The border of the tumor is indicated by arrows (hematoxylin and eosin stain; original magnification 20×).

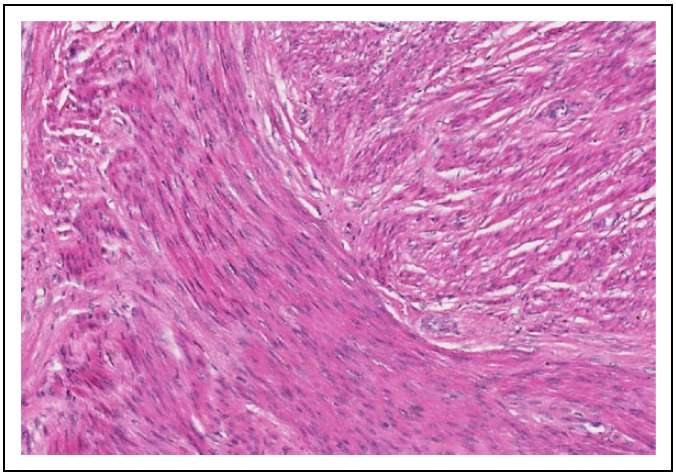

Figure 3. Uterine tumor (hematoxylin and eosin stain; original magnification 100×).

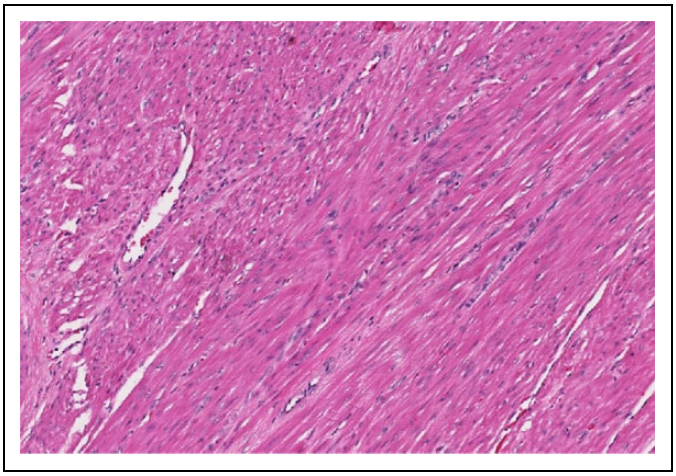

Figure 4. Normal myometrium (hematoxylin and eosin stain; original magnification 100×).

Compare an area from within the tumor (Figure 3) at higher power with the surrounding normal myometrium (Figure 4), viewed at the same magnification.

Comparing the tumor cells in Figure 3 with normal myometrial smooth muscle cells in Figure 4, would you be able to distinguish which image is from the tumor and which is from normal myometrium without the labels?

Distinguishing these 2 areas is very difficult. While the tumor may be a bit more cellular, this is a subtle change that only experienced pathologists might recognize. The point to be emphasized is that it is the presence of a mass, and not cytologic appearance, which allows one to recognize this lesion as a tumor.

Describe the cells of the tumor in more detail, utilizing the following criteria (and comparing these features to the normal myometrial cells).

Nuclear size: *Same as normal*
Nuclear:Cytoplasmic (N:C) ratio: *Same as normal*
Shape of nuclei (regular vs pleomorphic [variation in size and shape]): *regular elongated oval shape*
Nuclear chromatin staining (normochromatic versus hyperchromatic [increased staining on hematoxylin stain]): *Normochromatic*
Prominent nucleoli? *No*
Do you see areas of necrosis? *No*
Is it easy to identify mitotic figures? *No*; Abnormal mitoses? *No*
Therefore, what term would you use to describe the histological appearance of the cells in this tumor?
Well-differentiated.

Note: Well-differentiated is a term applied to the histological appearance of tumor cells. It means that the cells closely resemble their normal counterparts. The tumor cells in this case so closely resemble the normal myometrial cells that is difficult at high power to conclude that one is looking at a neoplasm (see Figure 3 vs Figure 4). Benign tumors are

typically well-differentiated. Malignant neoplasms may be well-differentiated but more often will show a range of decreasing differentiation that may progress to anaplasia (lack of differentiation). The histological features that are associated with decreased differentiation include increased nuclear-to-cytoplasmic ratio, pleomorphism of the nuclei and cells, hyperchromatism, and prominent nucleoli—none of which were observed in this case. Additional features suggestive of malignancy are increased mitotic activity (particularly in tissue that is not normally mitotically active), including abnormal mitotic figures, and the presence of necrosis (both grossly and/or microscopically), which were also not observed.

What is your pathological diagnosis?

Leiomyoma of the uterus (A benign tumor: leiomyo = smooth muscle; oma = benign neoplasm)

By your terminology above, you have identified the tumor as either benign or malignant.

Summarize the gross and microscopic morphological features in this case that support your classification.

Growth pattern: *Expansile, pushing, noninvasive growth*

Microscopic: *Well-differentiated; regular nuclear size and shape and normochromatic; absent or rare mitoses (less than 5 mitoses/10 high-power fields); absence of necrosis*.

Note: The classification of this tumor as benign implies absence of invasive local growth and inability to metastasize (discontinuous spread to distant sites). Nonetheless, benign neoplasms may be problematic and even fatal to the host due to growth in a sensitive location (eg, in the meninges or cardiac left atrium), other local effects (eg, ulceration in a hollow viscus), and secretion of indigenous or inappropriate hormones (ie, hormones that are normally not elaborated by the normal cellular counterpart of the tumor, resulting in a paraneoplastic syndrome).[1-2]

What is the natural history of this tumor?

Leiomyomas are common benign neoplasms of the uterus. Leiomyomas show expansile growth in the uterus. On cut section, they show a white, whorled appearance that gave rise to their colloquial term, fibroid. Ultrasonography is the standard diagnostic test. They generally show growth during reproductive years and regression in menopause. They may be asymptomatic but, depending on size, location, and number, may present with abnormal bleeding, urinary symptoms from compression of the bladder or rectum, pelvic pain, and interference with fertility and maintenance of pregnancy. Symptomatic leiomyomas may be treated surgically with hysterectomy or in a woman desiring pregnancy by myomectomy. Medical therapy includes hormonal therapy, uterine artery embolization, and radiofrequency ablation.

The malignant counterpart of leiomyoma is leiomyosarcoma (leiomyo = smooth muscle; sarcoma = malignant mesenchymal neoplasm). The histological appearance of leiomyosarcomas ranges from well-differentiated tumors that show increased numbers of mitotic figures to highly anaplastic tumors with areas of necrosis. These tumors show progressive invasive growth and metastasis. Leiomyosarcomas are believed to arise de novo from the myometrial cells. Leiomyomas are generally NOT considered to be premalignant, so most asymptomatic leiomyomas do not need be excised.[3-4]

Teaching Points

- Leiomyoma is a common benign neoplasm of the uterus.
- While frequently asymptomatic, leiomyomas may present with symptoms due to local expansion and compression within the uterus and/or into adjacent pelvic structures.
- Uterine leiomyomas are not considered to be premalignant.
- Benign neoplasms are characterized by expansile, smooth, and noninvasive borders.
- Histologically, benign neoplasms are well-differentiated, with regular cells and nuclei, rare mitoses, and absence of necrosis.

Declaration of Conflicting Interests

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Genetic Mutations and Multifactorial Inheritance: Dilated Cardiomyopathy

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, genetic mechanisms, developmental and functional abnormalities, mutations, cardiovascular, cardiomyopathy, dilated cardiomyopathy, disease mechanisms, genetic diseases, inherited diseases

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Primary Objective

Objective GM1.1: Types of Mutations. Describe different types of mutations that can occur in human disease, and discuss how each of these can produce abnormalities in DNA transcription and/or alterations in the type or amount of protein produced.

Competency 1: Disease Mechanisms and Processes; Topic GM: Genetic Mechanisms; Learning Goal 1: Genetic Mechanisms of Developmental and Functional Abnormalities.

Secondary Objectives

Objective GM1.5: Multifactorial Inheritance and Environmental Factors. Discuss and give examples of disorders associated with multifactorial inheritance and describe how environmental factors can interact with genetic factors to produce or modulate disease.

Competency 1: Disease Mechanisms and Processes; Topic GM: Genetic Mechanisms; Learning Goal 1: Genetic Mechanisms of Developmental and Functional Abnormalities.

Objective CH1.2: Cardiomyopathy. Compare and contrast the clinicopathologic features of dilated, restrictive, and hypertrophic cardiomyopathies.

Competency 2: Organ System Pathology; Topic CH: Cardiovascular—Heart; Learning Goal 1: Heart Failure

Patient Presentation

A 26-year-old male presents to the emergency department with complaints of a 5-month history of progressive dyspnea that became more severe over the past 6 days and prompts this evaluation. Medical history is significant for at least 6 upper respiratory infections over the past 2 years. Family history is significant for 4 cardiac-related deaths in ages between 24 and 38 years involving the 3 last generations of his family, as well as a 29-year-old paternal cousin with heart failure. There is no significant history of alcohol ingestion, toxin exposures, or illicit drug abuse. Physical examination discloses bilateral

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basal lung rales, displaced apical impulse to the left, systolic apical murmur, hepatomegaly of 6 cm below the right midclavicular line, and bilateral low extremity pitting edema extending to 5 cm above the ankles. Recorded vital signs are blood pressure = 105/65 mm Hg, Respiratory Rate = 28 per minute, Heart Rate = 138 per minute, and temperature = 98.9°F.

Diagnostic Findings

Echocardiogram shows marked cardiac enlargement, dilation of all chambers, 35% left ventricle ejection fraction, and left ventricle thrombi. Imaging studies show normal cardiac valves and patent coronary arteries. Laboratory studies reveal moderate B-natriuretic peptide elevations and mild troponin and liver enzyme elevations.

Questions/Discussion Points

What is Your Preliminary Diagnosis and Its Differential?

Dilated cardiomyopathy is the primary diagnosis, based on the clinical findings consistent with heart failure, cardiac enlargement of all chambers, imaging studies showing normal valves and patent coronaries, and functional studies describing decreased ejection fraction. The differential diagnosis based on the clinical findings includes other types of cardiomyopathy such as restrictive or hypertrophic, as well as multiple diseases included within the syndrome of dilated cardiomyopathy per se. Dilated cardiomyopathy can be further categorized as familial and inherited or as acquired. Acquired etiologies include myocarditis; toxins such as cocaine, amphetamines, or heavy metals; autoimmune; endocrine diseases such as hypothyroidism or hyperthyroidism; thiamine deficiency; and ischemic heart disease.[1,2]

What Clinical Considerations Should Follow a Diagnosis of Cardiomyopathy?

When suspecting a cardiomyopathy, the initial considerations are morphologic and functional, which help classify them as dilated, restrictive, hypertrophic, or one of the more unusual types of cardiomyopathy such as right ventricle arrhythmogenic or left ventricle noncompaction cardiomyopathy. Occasionally, these features may overlap or may not be fully developed, such as when you evaluate inherited genetic diseases early in their development.

The extent of organ involvement should be recorded. The manifestations may be limited to only the heart, but the disorder may affect other organs as well, such as skeletal muscle, kidneys or liver as part of the disease process, or may it affect other organs secondarily.

Constructing a pedigree tree may be very useful in determining the inheritance pattern. When evaluating the pedigree, it is possible that the information may be unknown or not investigated at the time of initial presentation. Genetics/familial considerations include autosomal dominant or recessive, X-linked, mitochondrial, or sporadic inheritance patterns which can easily be determined with the family history evaluation.[3]

Etiology of the cardiomyopathy should be investigated. This may include genetic, viral following a myocarditis, autoimmune, toxic, or unknown causes of cardiomyopathy.

The stage of heart failure at the time of presentation should be recorded using criteria of the American Heart Association or New York Heart Association.

What Pathophysiologic Mechanisms Are Involved in the Development of Dilated Cardiomyopathy?

Defects of force transmission, force generation, or calcium handling result in systolic dysfunction, cell death, and fibrosis, producing the dilated cardiomyopathy phenotype. Mutations involving δ-sarcoglycan may cause defects of force transmission; in a similar fashion, defects of force generation may be caused by mutations encoding for sarcomere proteins such as β-myosin.[4] Even in nonfamilial cases of cardiomyopathy, inherited genetic susceptibilities may determine how the cardiac muscle responds to environmental factors such as alcohol or viral myocarditis.

What Are the Inheritance Patterns of Dilated Cardiomyopathy? Can You Give Some Examples?

Approximately 30% to 48% of dilated cardiomyopathies are inherited or familial. Most of the inherited cases are autosomal dominant; but autosomal recessive and X-linked patterns have also been reported. Causative genes predominantly encode for sarcomere (ie, titin [TTN], actin, myosin, troponin) or cytoskeletal (ie, dystrophin, desmin, lamin) proteins. Dystrophin is the same protein involved in the X-linked Duchenne or Becker muscular dystrophies. Less commonly, an X-linked inheritance pattern may be identified in newborns and children as part of the Barth syndrome, which is caused by mutations of the gene tafazzin, which codes for an acyltransferase. Twenty percent of autosomal dominant, dilated cardiomyopathies identified genetically affect genes coding for TTN, a protein that provides structure, flexibility, stability, and chemical signals to the sarcomere.[5] These mutations result in an abnormally short TTN protein.[6] About 8% of all genetic dilated cardiomyopathy cases are caused by deletions or sequence variations of the LMNA gene that, when mutated or deleted, encode for an absent or abnormal lamin A/C protein. Most of these cases also have an associated atrioventricular block clinically, and in this circumstance, implantation of intracardiac defibrillator may be a consideration. Rare autosomal recessive cases result from mutations encoding for troponin I.

How Should You Proceed With the Genetic Evaluation of This Case?

Perform a careful pedigree analysis of all possible affected family members taking into consideration and annotating all possible involved cardiac and extracardiac clinical features. Inherited cardiomyopathies are phenotypically variable in regard to the age of presentation, expressivity, or disease

progression. Mixed forms that do not fit into a single traditional category have been described as several instances of dilated cardiomyopathy have been associated with an arrhythmogenic phenotype. Incomplete penetrance and variable expressivity warrant a high index of suspicion, particularly for first-degree relatives. You may consider genetic testing for first-degree family members, with the caveat that the yield may be much lower than in the cases of hypertrophic cardiomyopathy. The sensitivity of genetic sequencing panels for familial dilated cardiomyopathy cases is 25% but rises up to 40% if the cardiomyopathy coexists with conduction defects. A truncated TTN protein caused by TTN frameshift, nonsense, or splice mutations have been reported in approximately 25% of familial dilated cardiomyopathy cases. Titin encompasses 363 exons with an established role in muscle assembly and function. At present, there seems to be no clear correlation between genotype and phenotype probably because this large gene can undergo extensive alternative splicing. These splicing variants beg for a more refined interpretation of genetic findings.[7] Truncating mutations have also been associated with sporadic cases, suggesting increased susceptibility to environmental effects. The significance of genetic variations is unknown in many instances. Frequently, a genotype–phenotype correlation will be of limited clinical utility in the treatment of the patient, but some instances warrant genetic characterization.

Teaching Points

- Clinical evaluation including complete pedigree analysis is essential in the evaluation of genetic disorders such as dilated cardiomyopathy.
- Penetrance and expressivity are important considerations, especially when evaluating first-degree relatives.
- A truncated protein that fails to transmit or generate force within or across the sarcomere or adequately handle calcium can result from frameshift, nonsense, or splice mutations.
- The clinical significance of mutations is frequently unknown.
- Many dilated cardiomyopathy cases are familial; most commonly autosomal dominant disorders, but autosomal recessive and X-linked inheritance patterns can also be observed.
- Dilated cardiomyopathy clinical presents with heart failure and cardiac enlargement; imaging studies showing normal valves and patent coronaries and a decreased ejection fraction.

Authors' Note

The opinions expressed herein are those of the authors and are not necessarily representative of those of the Uniformed Services University of the Health Sciences (USUHS), the Department of Defense (DOD), or the United States Army, Navy, or Air Force.

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Benign Papilloma of the Breast

Moshe Sadofsky, MD, PhD[1]

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, disease mechanisms, organ system pathology, basement membrane, benign, breast, neoplasia, papilloma

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Primary Objective

Objective N2.1: Prevalence and Geographic Impact on Neoplasia. Describe the prevalence of neoplastic diseases and discuss the environmental factors that influence patients as they move between geographical regions.

Competency 1: Disease Mechanisms and Processes; Topic N: Neoplasia; Learning Goal 2: Environmental Influences on Neoplasia.

Secondary Objectives

Objective N2.2: Mechanisms of DNA Damage Repair. Describe the mechanisms by which exposure to radiation, tobacco, alcohol, or other environmental chemical agents can produce cancer.

Competency 1: Disease Mechanisms and Processes; Topic N: Neoplasia; Learning Goal 2: Environmental Influences on Neoplasia.

Objectives N3.1 through N3.5. Learning Goal 3: Characteristics of Neoplasia. Apply knowledge of the characteristics of neoplasia to discuss the morphologic appearance, classification, biological behavior, and staging of neoplasms.

Competency 1: Disease Mechanisms and Processes; Topic N: Neoplasia.

Objective BR1.1: Clinical Presentation of Breast Lesions. Identify the most frequently diagnosed breast lesions by age of the patient, based on the most common clinical presentations in males versus females.

Competency 2: Organ System Pathology; Topic BR: Breast; Learning Goal 1: Nonneoplastic Disorders of the Breast.

Objective BR1.4: Fibrocystic Change. Discuss the clinical significance of proliferative and nonproliferative fibrocystic change, with and without atypia, and describe how each of these changes and the family history affects the subsequent risk of developing breast cancer.

Competency 2: Organ System Pathology; Topic BR: Breast; Learning Goal 1: Nonneoplastic Disorders of the Breast.

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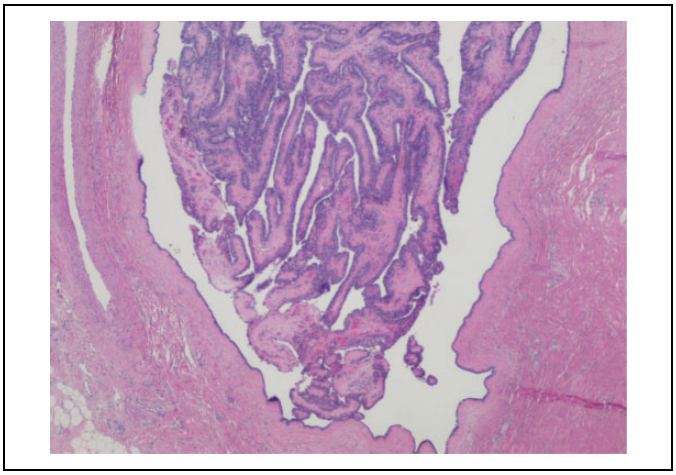

Figure 1. Low-power H&E image from core biopsy of breast.

Patient Presentation

A 37-year-old woman presents to her physician with a palpable density in her left breast. She noticed it 1 month ago and it hasn't changed in size. Her medical history is unremarkable. Medications include oral contraceptives. On examination, she appears somewhat anxious. Her vital signs are within normal limits. Physical examination is remarkable for an ill-defined area of firmness in the left breast in the upper outer quadrant adjacent to the nipple. The region is not tender, and there is no inflammation or discharge. A breast ultrasound core biopsy is obtained.

Questions/Discussion Points, Part 1

Before jumping to the histologic sections, it is worth discussing the differential diagnosis based on the patient presentation.

What is the differential diagnosis of a palpable breast mass?

Our thinking is guided by the history. Is there pain? If so, is it within the breast or associated with the chest wall? Does it change with the hormonal cycle? Is there nipple discharge, and if so, what is its character? These distinctions help determine the likelihood of a true neoplasm of breast origin versus other physiologic possibilities. A thorough discussion is available in the study by Santen. Most importantly, 90% of new nodules presenting in premenopausal women are benign. In younger women, these are usually fibroadenomas, while "in the later reproductive period, hyperplasia, cysts, and carcinoma in situ are more common".[1] As occurs elsewhere in the body, growths may also originate in nonglandular tissues including lipoma, fat necrosis (with a history of injury), and hemangioma. Imaging might suggest an area of increased density within the breast, not explained as simple cyst.

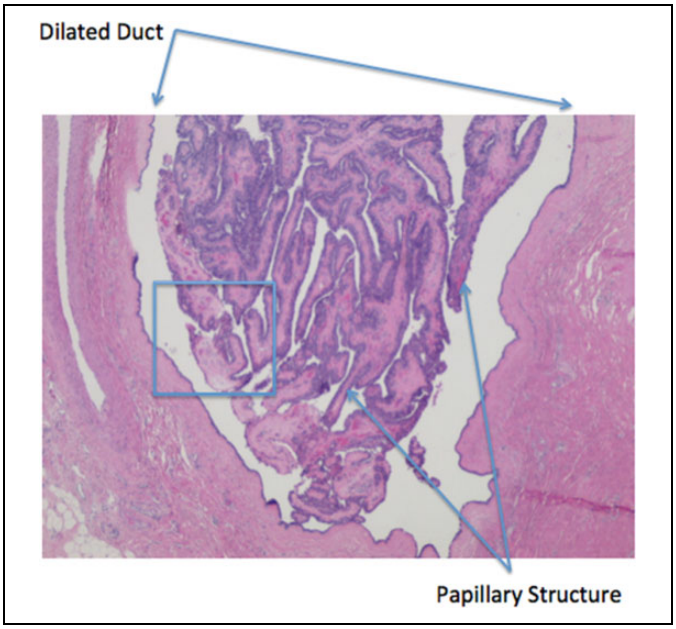

Figure 2. The image of Figure 1 is labeled showing the central papillary structure. A box encloses the region magnified below.

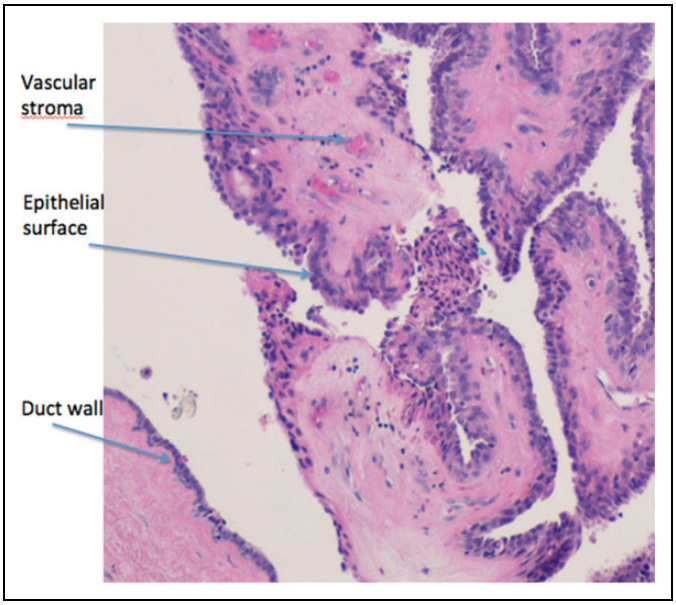

Figure 3. The comparison of the epithelial surface of the central fronds shows a monolayer of basophilic cells similar in appearance to the ductal lining and a fibrovascular eosinophilic stroma.

The biopsy was obtained (Figure 1). Describe the histologic features of this lesion. What is your diagnosis and what is its biologic behavior?

The low-powered Hematoxylin and Eosin (H&E)-stained slide obtained from the biopsy contains the field in Figure 1. Within a large dilated duct sits a structure folded into papillary fronds lined by a basophilic epithelium surrounding

a pink central fibrovascular stroma. These features are labeled in Figure 2.

A box in Figure 2 is seen at higher magnification in Figure 3. Figure 3 shows the duct wall and the epithelial surface of the papillary fronds to be composed of similar cells, forming a simple layer resting upon a basement membrane. The latter is not easy to see directly with these dyes but can be visually enhanced with special stains. Both tissues have matured in the manner characteristic for ductal tissue, with a polarized surface facing the duct lumen. The fronds also contain a stroma and small blood vessels. The structure is named an "intraductal papilloma."

What Does the Name Tell You?

This is a benign proliferation in some ways analogous to adenomas that may occur elsewhere. If it had been malignant, the name would have included the word "carcinoma." Papillomas have 2 main clinical presentations including solitary lesions near the nipple or multiple peripheral papillomas. The latter have a higher rate of atypia or malignancy arising in them. The most important observation is that there is no evidence of invasion. In other words, the epithelium does not penetrate the basement membrane and spread into adjacent areas. This proliferative neoplastic process can be associated with an increased risk of cancer in the future, especially if there is atypical piling up of the epithelial cells on each other (not seen here). In the absence of invasion, this lesion is benign and does not need further treatment. However, the patient should remain alert for changes in the future.

An additional important feature worth remembering is that neoplasia (new growth) includes benign lesions. These may grow to large size and can even become life threatening if they interfere with a function (eg, benign meningioma). Benign doesn't mean, "you can live with it." It means "not invasive."

Other Manifestations of Benign Breast Disorders

Most important, benign lesions of the breast are much more common than malignancies. The incidence of these disorders changes with the age of the patient. An online review of Benign Breast Disease in Women is referenced.[1]

Benign lesions of the breast are often classified in terms of their potential contribution to future breast cancer. In this light, there are 3 common categories:

- Nonproliferative changes (with little to no increased risk of cancer). This includes fibrocystic change and cysts;
- Proliferative lesions without atypia, including this case;
- Proliferative lesions with atypia.

Proliferative disease is associated with a 1.5- to 2-fold increased risk, while proliferative disease with atypia confers a 4- to 5-fold increased risk.[2]

What is the structure and function of the basement membrane that separates the epithelium from the fibrovascular core?

It is widely recognized that all epithelia organize themselves on a structure called the basement membrane. However, the relationship of the cell to this structure is much more interesting and active than many appreciate. Studies reveal "common functions that include the induction and maintenance of cell polarity, the establishment of barriers between tissue compartments, the organization of cells into tissues, and the protection of adherent cells from detachment-induced cell death, anoikis."[3] Although the term membrane is used, it is not a lipid membrane as the term is used elsewhere. Rather, the basement membrane is a complex type of extracellular matrix with an elaborate organization that includes collagen IV, laminins, other connective proteins and heparin sulfate containing proteoglycans. The absolute identity of the components of the basement membrane varies among cell types and are essential for the growth and maintenance of all epithelia.

Teaching Points

A quick review of the normal histology of ductal tissue in the breast shows a simple monolayer of epithelial cells with an underlying basement membrane.

- Despite the proliferative classification of this papilloma, the basement membrane is not violated, so there is no invasion.
- Invasion is an essential hallmark of epithelial malignancy.

Benign lesions of the breast, depending on their microscopic properties, may range in future risk of developing cancer from none at all, to a 4- to 5-fold increase.

Acknowledgment

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Lead Poisoning

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, disease mechanisms, environmental mechanisms, occupational exposure, lead poisoning, cell injury

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Primary Objective

EM1.5: Occupational Exposure. Provide examples of industrial, occupational, or environmental exposures that produce disease, the resultant pathologic changes in these affected organs from chronic exposure, and indicate what organ systems are most commonly affected by which agents.

Competency 1: Disease Mechanisms and Processes; Topic EM: Environmental Mechanisms; Learning Goal EM1: Cell Injury.

Patient Presentation

A 7-year-old boy is brought to the clinic by his mother with complaints of increased irritability, vague abdominal pain, and constipation. The child had been well until these vague symptoms began approximately 6 months earlier, and these symptoms are becoming more frequent. The school has informed the parents that their child has difficulty paying attention in class over that past few months. The family lives in an inner-city home. The child has 3 younger siblings.

On physical examination, the child appears well developed and well nourished. He is in the 40th percentile for height and weight. He had measured in the 50th percentile 1 year ago. He is alert and oriented. He has mild tenderness elicited by abdominal palpation; the remaining examination is unremarkable.

Diagnostic Findings

Complete blood count (CBC) is given in Table 1.

Questions/Discussion Points

Given the Clinical History, What Is a Broad Differential Diagnosis?

The differential diagnoses include attention-deficit disorder, lead toxicity, iron deficiency anemia, fetal alcohol syndrome, thyroid disorder, hypercalcemia, and pituitary disorders. One could also consider vision or hearing impairments. The CBC findings will help narrow this differential.

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Table 1. Complete Blood Count.

Hematocrit	28%
Hemoglobin	8 g/dL
WBC	5300/mm^3
Neutrophils, segmented	65%
Eosinophils	2%
Lymphocytes	25%
Monocytes	8%
Platelet count	150 000/mm^3

Note. Microscopic Review Reveals Microcytic Hypochromic Anemia With Basophilic Stippling.
Abbreviation: WBC, white blood cells.

What Is the Most Likely Diagnosis in This Child?

With the behavioral changes, irritability, vague abdominal complaints, decreased growth, and microcytic hypochromic anemia with basophilic stippling, lead toxicity must be considered very high in the differential diagnosis. This can be confirmed with laboratory testing. In our patient, 32 μg/dL of lead was found in the blood. As early detection can be subtle, constant vigilance of the primary care provider is necessary. It is important when patients present with attention-deficit disorders to be sure to rule out organic causes.

What Are the Risk Factors for Lead Poisoning?

There are multiple environmental risk factors for lead poisoning. Leaded gasoline was banned in the United States in 1996, but deposits may still be found in the soil. The amount of lead allowed in decorative paints intended for household use was markedly reduced in the United States as of 1978.[1] Lead is still used in many other products. These can include imported items such as toys, furniture, ceramics, crystal ware, "traditional" medicines, and spices. Even cosmetics may contain variable amounts of lead. Occupational exposure from employment in mining, metallurgy, construction, battery manufacture, and recycling can contaminate the clothes of employees who may inadvertently bring lead containing dust home. Recent events have highlighted the dangers of lead pipes for water or copper pipes that have lead soldering which can leak lead into drinking water. High levels of lead have also been found when certain ceramics are used that have a lead-based paint or glaze, especially products from Mexico or China. Other less common risk factors include artists making stained glass artifacts or windows, as this requires lead soldering.

What Are Acceptable Levels of Lead?

In 2012, the Centers for Disease Control (CDC) chose 5 μg/dL[2,3] as the reference level at which clinical intervention should be taken to limit additional exposure to lead. It is important to note that it is not a toxicologic threshold, as no safe blood lead level has been determined. This level identifies the 2.5% of children with the highest blood lead levels based on US survey data collected prior to that year. More recent survey data have found that the value for this cutoff has dropped to ~4 μg/dL. Ultimately, the CDC will continue to adjust the value of this cutoff as new epidemiologic data become available. Interventions to prevent further lead accumulation, which are also appropriate as measures to prevent lead poisoning from initially occurring, include identifying and eliminating the sources of exposure, changing the behavior that leads to ingestion of lead-containing materials (nonnutritive hand/mouth activity), and the correction of any nutritional deficiencies, particularly those of calcium, iron, and vitamin D.[4] Chelation therapy (drugs to enhance a lead diuresis) may be added if blood lead levels above 45 μg/dL are found.

How Can You Make a Diagnosis of Lead Poisoning?

Anemia often is observed in young lead-poisoned children. One should remember that a microcytic, hypochromic anemia will most often be found in patients with iron deficiency anemia or alpha-thalassemia. Examination of a blood smear looking for basophilic stippling may be very useful to separate the causes of anemia in some patients. The confirmation is made by obtaining a blood lead level as described earlier.

What Organ Systems Can Be Involved With This Disorder?

Lead toxicity can affect multiple organ systems at the biochemical, subclinical, and clinical levels. The findings are related to the blood lead level. At the biochemical level, toxicity to many enzymes has been documented. As the level of lead in the blood rises over 10 μg/dL, the levels of 1,25-dihydroxyvitamin D fall. This is the active hormonal form of vitamin D and is necessary for efficient intestinal absorption of calcium. Three of the 8 enzymes necessary for heme production are inhibited by lead, beginning at levels as low as 10 μg/dL for the most sensitive enzyme, delta-aminolevulinic acid dehydratase. When the last enzyme in the pathway, ferrochelatase, is impaired, the precursor molecule protoporphyrin accumulates in the cell. Measurement of erythrocyte protoporphyrin levels in peripheral blood samples may be a useful clinical tool for following toxicity in patients with lead levels over 20 μg/dL. In studies of children, cognitive scores, hearing, and growth have all been found to be inversely related to blood lead levels. However, at lower lead levels, these would be subclinical findings, that is, not presenting with symptoms. At higher levels, >20 μg/dL, lead can be associated with chronic or recurrent abdominal pain and constipation, loss of appetite, attention deficits, and hyperactivity. In rare cases, peripheral nerves may be impaired, resulting in weakness of the arms and legs, but this is more typically seen in adults with chronic severe lead poisoning. Chronic lead poisoning may uncommonly be associated with a "lead line" in the mouth: This is a line of hyperpigmentation on the gingiva adjacent to the teeth. At much higher levels of lead, over 100 μg/dL, encephalopathy and death can occur. One may have acute poisoning from very high levels of lead exposure, but much more common are the chronic lower levels of exposure

to lead. The skeletal system may show increased radiodensities at the ends of the long bones at the metaphyses. The renal system may show chronic tubulointerstitial disease over time with high lead levels. Adults with chronic lead exposure may show demyelination of the peripheral nerves.

How Would You Describe the Changes Seen in the Blood Smear of a Patient With Lead Poisoning?

One of the more common systems involved with lead poisoning is the hematologic system where one can find anemia, red blood cells with basophilic stippling (which is one of the hallmarks of diagnosis), and ring sideroblasts on bone marrow evaluation. The anemia most often found is a microcytic, hypochromic anemia, but this is likely due to other causes such as iron deficiency. The mechanism of the ring sideroblasts is related to the accumulation of iron-laden mitochondria in the red blood cell precursors due to the inhibition of ferrochelatase by lead.

What Is the Mechanism of Lead Poisoning?

Lead is a heavy metal that binds to proteins potentially altering their function. It competes with essential metals such as calcium for binding sites. In test tube studies, many calcium-binding proteins have a higher affinity for lead than calcium. These can result in multiple effects. For example, neurotransmitter release is a calcium-dependent process perturbed by the presence of lead. In children, over 70% of retained lead resides in the skeleton from which it can be released very slowly over years to decades after cessation of further ingestion.

Is Lead Absorption the Same for Children and Adults?

No. Lead compounds are poorly dissolvable in water. Lead absorption is dependent on the gut's ability to digest lead-containing material; this is enhanced in acidic environments like the stomach. Like calcium, lead is absorbed more efficiently in children than adults. In children, over 50% of the digested lead (lead in solution) can be absorbed via the intestinal tract compared to 15% in adults.

What Are Possible Treatments of Lead Poisoning?

For acute ingestion, a gastric lavage could be performed to decrease the amount of lead-containing objects still in the stomach. Cathartics can be given to rapidly remove lead already further into the intestinal tract. For chronic ingestion, chelation therapy may be necessary for lead levels of $\geq$45 μg/dL as per CDC/American Academy of Pediatrics (AAP) recommendations. Treatment successfully improves biochemical profiles; however, less data support the reversibility of neurocognitive effects of lead. In all cases of increased lead levels, treatment should include identification and elimination of the source of the lead, behavior modification to limit ingestion, and nutrition maximization.

Teaching Points

- Low lead levels, under 10 μg/dL, can have permanent neurologic effects in children, especially contributing to attention deficit disorders and decreased cognitive abilities.
- Higher lead levels can affect multiple organs such as its long-term accumulation and retention (over years) in bone and teeth while causing toxicity in the bone marrow with shortened red cell survival and the development of microcytic hypochromic anemia with basophilic stippling; central nervous system complaints of difficulty learning and focusing; decreased renal function; and gastrointestinal complaints of abdominal pain and constipation.
- Chronic low levels of exposure are much more common than acute high levels of toxicity.
- A high degree of vigilance is required to suspect lead toxicity, especially in children where absorption of lead is higher than in adults.
- Risk factors for lead toxicity include the ingestion of environmental sources of lead such as in drinking water, lead paint or the dust derived from that paint, contaminated soil as well as secondary exposure from occupational hazards such as workers from foundries, paint manufacture, or battery factories.
- The mechanism of lead poisoning centers around its affinity for proteins and its competitiveness with essential metals to protein-binding sites.

Authors' Note

The opinions expressed herein are those of the authors and are not necessarily representative of those of the Uniformed Services University of the Health Sciences (USUHS), the Department of Defense (DOD), or the United States Army, Navy, or Air Force.

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Autosomal Recessive Inheritance: Cystic Fibrosis

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology, competencies, cystic fibrosis, developmental and functional abnormalities, disease mechanisms, genetic mechanisms, inheritance patterns

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Primary Objective

Objective GM1.2: Inheritance Patterns. Compare and contrast the inheritance patterns of different types of Mendelian disorders and give examples of each type of pattern.

Competency 1: Disease Mechanisms and Processes; Topic GM: Genetic Mechanisms; Learning Goal 1: Genetic Mechanisms of Developmental and Functional Abnormalities.

Patient Presentation

A 22-year-old Caucasian male presents with a recurrent cough. He has had frequent respiratory illnesses and abdominal discomfort throughout his life. He has always been on the lower range of normal for height and significantly smaller than his siblings. His current primary care physician found his lung examination to be abnormal (wheezing and crackles) as well as an absence of the vas deferens on genitourinary examination.

Diagnostic Findings, Part 1

What is Your Differential Diagnosis Based on the Clinical History?

The patient presents with signs and symptoms that are classical for cystic fibrosis (CF). Some similar findings (short stature and chronic lung infections) may be seen in other disease states, such as primary ciliary dyskinesia (Kartagener syndrome) as well as asthma and should be excluded in this patient. In CF, progressive scarring ultimately leads to atrophy of the vasa deferentia.

Questions/Discussion Points, Part 1

What Testing is Available for this Patient and Which is Recommended?

Cystic fibrosis results from loss of function of the CF transmembrane conductance regulator (CFTR) protein caused by mutations in the *CFTR* gene. The classic diagnostic test for CF is the measurement of sweat chloride levels. This would be the recommended test for a patient suspected of being affected with CF.

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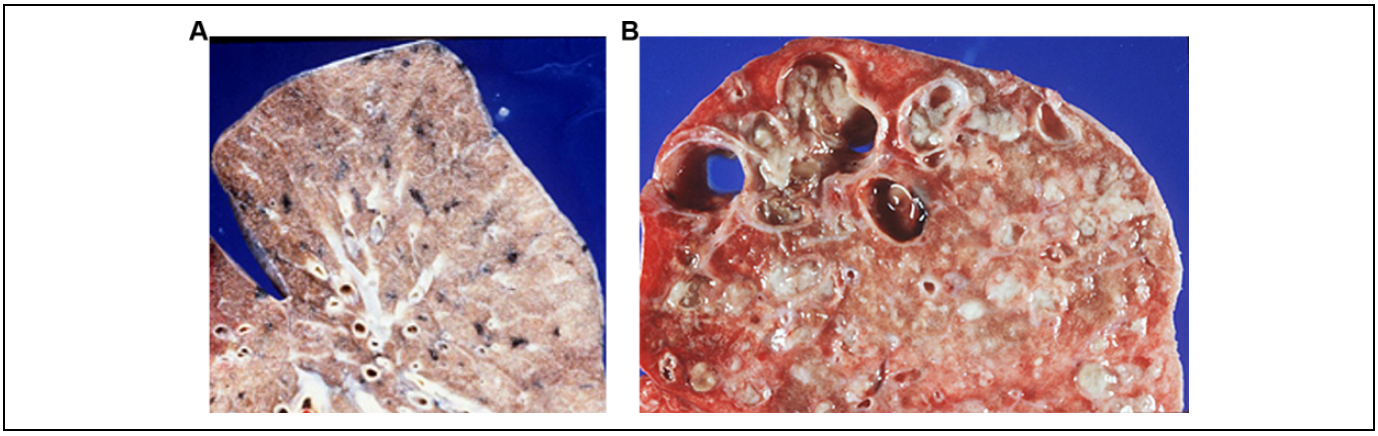

Figure 1. Autopsy findings. A, Normal lung. B, Lung affected by cystic fibrosis.

Biochemical screening tests for newborns typically measure plasma levels of immunoreactive trypsinogen (a proenzyme that builds up in the blood due to disease-related pancreatic duct dysfunction). These tests are advantageous for screening neonates as they demonstrate high sensitivity, can be run on dried blood spots, and proenzyme levels are altered regardless of the specific etiologic genetic alteration.

Genetic screening tests are useful for expectant parents to determine the "carrier status" of each parent and to assess the risk that a child born to them might be affected by CF. Since many genetic tests only evaluate a subset of all possible pathogenic mutations, patients must be counseled regarding the small residual possibility of having an affected child.[3]

Explain the Inheritance of CF and Show How It is Possible for an Individual to Inherit a Mutation in Each CFTR Allele and Present With No Disease, Mild Disease, or Severe CF

Cystic fibrosis is the most common, lethal, inherited disease in white populations. Approximately 1 in 2500 newborns in the United States is born with the disease.[1] It typically displays autosomal recessive inheritance requiring each parent to provide a pathogenic allele to their child for the disease to manifest. A single genetic mutation is responsible for 70% of cases and consists of a 3-base pair deletion leading to a loss of phenylalanine at codon 508 (ΔF508 or del508). The ΔF508 mutation displays classical Mendelian inheritance, whereby 2 carrier parents (each heterozygous for ΔF508) would have an expected risk of having an affected child of 25% for each pregnancy (25% risk unaffected and 50% risk of carrier offspring). Not all parents will carry identical mutations and a child may therefore inherit different mutations from each parent, with differing impacts on the CFTR protein. This is one reason a spectrum of disease phenotypes may be observed. Additionally, some mutations may only demonstrate a partial effect, which may only create a CF phenotype when identified in concert with other specific mutations (R117 and poly[d]). This complexity and the current identification of over 1800 described mutations in the *CFTR* gene produce wide variability in the effect that a given mutation will have on protein function and ultimately on the clinical phenotype.

Explain the Normal Physiologic Function of the CFTR Protein and Which Tissues are Affected by the Loss of CFTR Function

The CFTR protein is an ion channel protein regulating chloride concentrations across epithelial surfaces. In a healthy individual, negatively charged Cl^- ions are passively transported through the membrane via the CFTR. Water can then passively diffuse through the membrane to areas of high solute concentration producing typical mucus. The absence of a functional CFTR protein, either by a mutation that fails to transport it to the membrane or a mutation within a membrane-bound protein itself, leads to the inability of chloride to move outward and chloride becomes sequestered within the cell along with high concentrations of sodium. Since the movement of water passively follows solute concentration, secreted mucus in affected patients becomes viscous and tenacious leading to complications of transport.[2]

The CFTR also exists within the eccrine sweat glands of the skin to balance the reabsorption of sodium and chloride (salt) from initially excreted fluid. In the absence of a functional CFTR, the reabsorption of sodium chloride is ineffective and the amount of Na^+ and Cl^- in the excreted sweat remains high. The CFTR channel exists in many other tissues as well; however, the effects on the lungs and digestive tract become most clinically apparent in an affected patient.[1]

Describe the Pathophysiologic Process that Occurs in the Lungs of Patients with Severe CF that Leads to Bronchiectasis and Chronic Pneumonia Including a Description of the Histopathology as the Disease Progresses

The more viscous secretions produced by failure of water to thin the mucus covering the lung epithelium inhibits

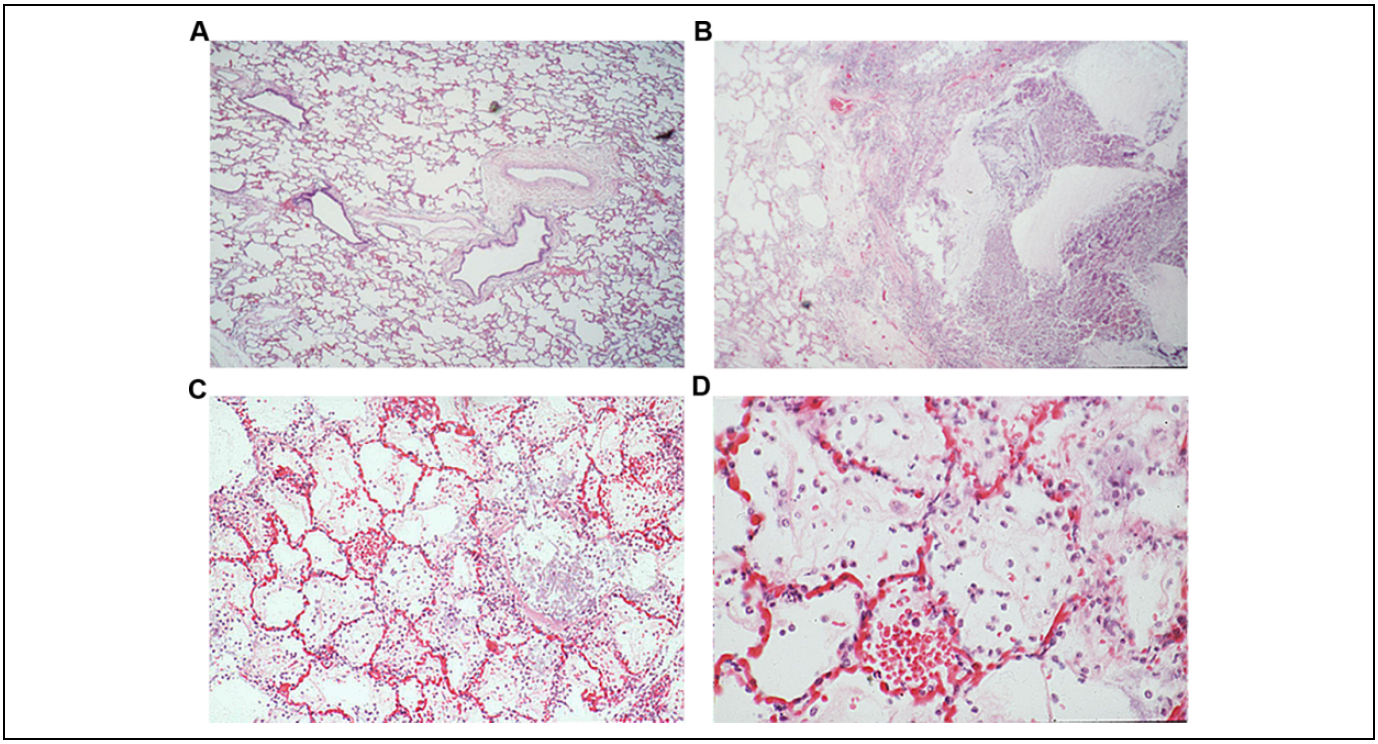

Figure 2. Histopathology. A, Normal Lung with patent airspaces. B, Extensive mucopurulent secretions in dilated airway. C, Alveolar lung parenchyma with mucus and acute and chronic inflammation. D, Higher power view of C demonstrating the mixed inflammatory infiltrate associated with cystic fibrosis.

mucociliary clearance and causes mucus plugging of the airways. This in effect seals off the terminal airspaces. Inhaled bacteria cannot be cleared effectively and chronic infections are the result. The body's attempts to contain these infections lead to an exuberant inflammatory response, progressive fibrosis, dilatation, and ultimately destruction of the airways.

Case continued—During the next year, the patient develops a severe pneumonia and is hospitalized. Respiratory cultures grew out *Pseudomonas aeruginosa* and the patient's oxygenation continued to decline. Antibiotics could not clear the patient's infection, and he was placed on ventilator support but ultimately progressed and died.

Diagnostic Findings, Part 2

Compare and Contrast the Gross Pathology in Figure 1A and B

A. Normal Lung: Note the spongy appearance of the cut surface and gradual tapering of airways toward the periphery of the tissue. The surface has a "dry" appearance as it is actually made up of numerous tiny alveoli.
B. Lung affected by CF: Bronchiectasis (airway space enlargement with associated wall thickening) with bronchi filled with excessive mucopurulent secretions is seen. The secretions give a more "glossy" appearance to the cut surface. Note also the peripheral coalescence of airspaces with mucoid containing cyst-like spaces. These become continually infected and fibrotic over the course of the disease, hence, the given name of the disease, "cystic fibrosis".

Compare and Contrast the Histopathology in Figure 2A-D

Panel A demonstrates a low power view of a slide from a healthy individual. The majority of airspaces are intact and lined by thin walled alveoli. The bronchioles present are patent and are typically composed of a low columnar to cuboidal epithelium. Panel B demonstrates a similar power view from an individual affected by cystic fibrosis with abundant mucopurulent material within an expanded airway. Panels C and D show higher power views of the mixed inflammatory infiltrate which is seen within the individual alveoli in patients affected with cystic fibrosis.

Questions/Discussion Points, Part 2

What Therapies May Minimize the Symptoms of CF?

There are a variety of biomechanical techniques that are aimed at clearing the thickened mucus from the airways and often involve some forms of percussion or vibration. Several

categories of medications are also available to aid in fighting infections, thinning mucus, and in some cases (given specific causative mutations) potentiating the CFTR channel to allow for increased chloride transport.

What are Some Possible Therapies that have a More Definitive Impact on the Disease?

The severe damage caused by the course of the disease leaves few medical options for improved pulmonary function; however, for some patients, lung transplantation can provide a much more definitive impact on lung function as well as the overall survival. Most importantly, however, lung transplantation is not a "cure" as it only alleviates the pulmonary symptoms of the patient. The other organs affected by the disease are not modulated by a transplant.

Recent investigations involving large-scale mathematical and chemical libraries have identified several possible drug molecules that target precise causes of the disease created by individual mutations. Given the diverse impacts the various CF mutations can have on protein production, processing, and regulation, it is not surprising that different drugs are necessary to provide differing corrective effects. Some drugs work by increasing shuttling of the CFTR to the membrane, while others act to improve chloride transport through the CFTR and even others attempt to overcome nonsense mutations by allowing the ribosome to "read through" premature stop codons during translation.[4]

Given that the disease is inherited in a patient's DNA and many of the causative genetic mutations have been elucidated, there is a possibility that in the future, site-directed gene editing may hold promise for a broader therapy unique to the patient's own disease and impacting and improving all affected organ systems.

Teaching Points

- Cystic fibrosis is the most common inherited autosomal recessive disease in the Caucasian population.
- The disease affects multiple organ systems and can have a wide variety of clinical presentations.
- Genetic mutations of the CFTR gene lead to an ineffective chloride transporter that explains many of the clinical symptoms.
- There is hope that modern technological advancements could lead to not only symptomatic control but also possibly even cures for the disease in the future.

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Educational Case: Fibroadenoma of the Breast

H. James Williams, MD[1]

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, disease mechanisms, breast, neoplasia, fibroadenoma, palpable breast lesion, mammographic findings, phyllodes tumor

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Primary Objective

Objective BR2.1: Fibroadenoma and Phyllodes Tumor. Compare and contrast fibroadenoma and phyllodes tumor in terms of clinical features, morphologic findings, and prognosis.

Competency 2: Organ System Pathology; Topic BR: Breast; Learning Goal 2: Molecular Basis of Breast Neoplasms.

Secondary Objective

Objective N3.1: Morphologic Features of Neoplasia. Describe the essential morphologic features of neoplasms and indicate how these can be used to diagnose, classify, and predict biological behavior of cancers.

Competency 1: Disease Mechanisms and Processes; Topic N: Neoplasia; Learning Goal 3: Characteristics of Neoplasia.

Patient Presentation

A 37-year-old woman presents to her physician with concern about a left breast nodule she recently discovered on self-examination. The patient states that the nodule is approximately 2 cm in size, close to her left axilla, and feels firm. She is concerned because her mother, age 54, was recently diagnosed with breast cancer.

Questions/Discussion Points, Part 1

What Pertinent Questions Should be Asked as Part of the Detailed History Prior to Physical Examination?

How long has the nodule been there? If the lesion developed very recently, one could choose to follow the lesion for a short time to see if it persists.

Has it changed in size over time? Change in size could include decreasing, increasing, or fluctuating lesions. Fluctuation in size would be suggestive of menstrual effect or fibrocystic change. A decrease in size might indicate a cyst getting smaller. An increase in size would be more worrisome for a more serious lesion.

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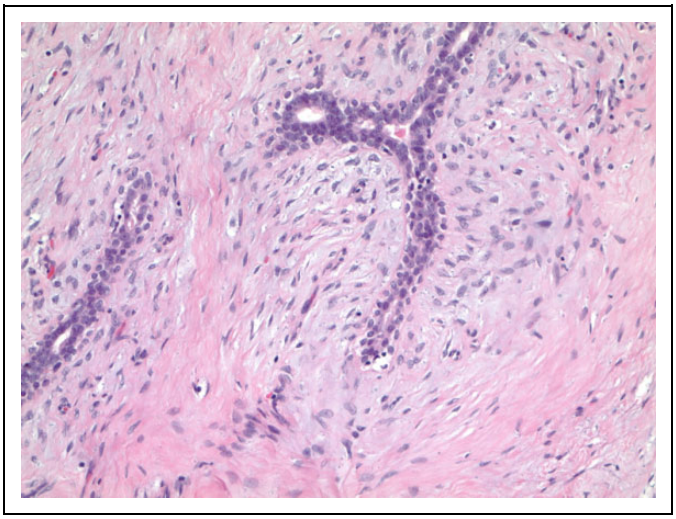

Figure 3. Microscopic image of left breast nodule at high power, H&E 20×. The stroma of the lesion has low cellularity with no mitoses or cytologic atypia. The epithelial component shows bland cytologic features with associated myoepithelial cells.

Is the nodule painful? Malignancies are not typically painful; however, inflammatory lesions can be painful as could benign lesions.

Has there been nipple discharge and if so, is it bloody? Bloody nipple discharge may be associated with an intraductal papilloma or, more rarely, cancer. A finding of nipple discharge would need to be investigated more carefully.

Does anyone in your family have or have had breast cancer? If there is a family history of breast cancer, what is the relationship of the family member with the patient (ie, is it the patient's mother, sister, or daughter)? Also, what was the age at time of diagnosis of the family member? Younger age of breast cancer would be much more concerning for a possible familiar component of a breast cancer than breast cancer in an older first-degree relative. This question is addressing the associated increased risk of malignancy and/or hereditary disease in close relatives, especially if they developed breast cancer at a young age.

On physical examination of the patient's left breast, what findings would favor either a benign or malignant diagnosis? Physical examination can be helpful, as some features are more common with benign or malignant lesions. Features of benign neoplasms include the following: multiple indistinct nodules (lumpy breast) that favor fibrocystic changes and lesions beneath the nipple which may suggest an intraductal papilloma.

However, a fixed, irregular, and firm mass is suspicious for malignancy as is dimpling of the overlying skin. Another important factor is location of the lesion within the breast, as 50% of breast cancers arise in the upper outer quadrant; thus, lesions in this area would be more suspicious for malignancy.

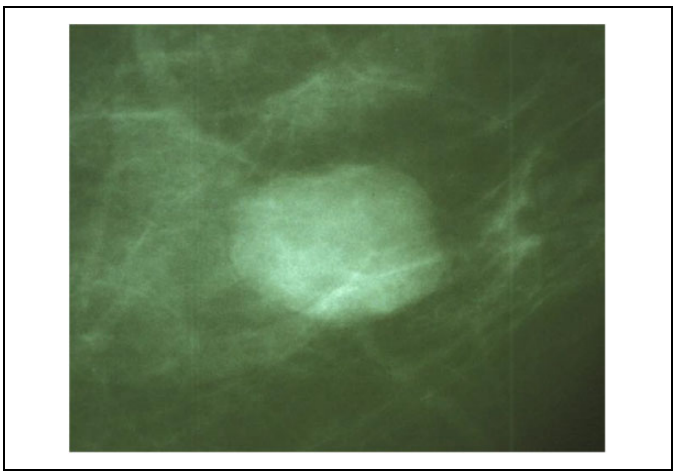

Figure 1. Mammogram of left breast nodule. The lesion is homogeneous and is sharply demarcated from the normal breast tissue.

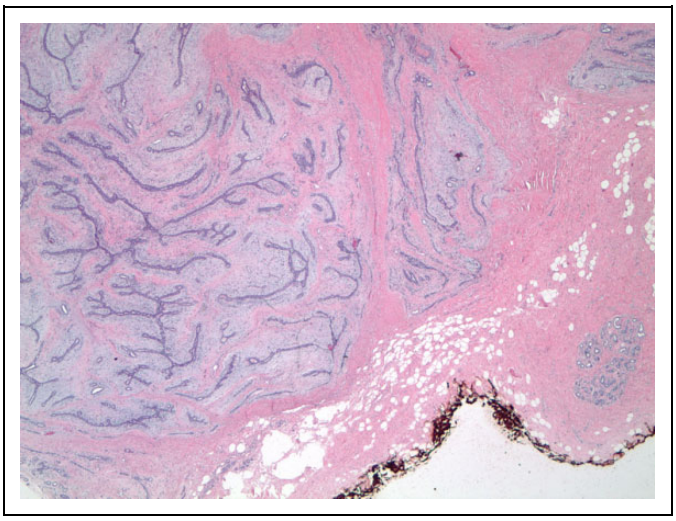

Figure 2. Microscopic image of left breast nodule at low power, H&E 2×. On low power, the lesion is seen to be sharply demarcated from the adjacent normal breast tissue.

Diagnostic Findings, Part 2

The patient undergoes mammography of the left breast nodule. The mammography is shown in Figure 1.

Questions/Discussion Points, Part 2

What Radiographic Findings in Figure 1 Are Seen, and Do They Favor a Benign or Malignant Diagnosis?

Similar to physical examination, radiologic examination is important in working up breast lesions. Several factors are more suggestive of benign versus malignant lesions. The following findings favor a benign process when they

are present: sharp distinct borders, homogenous texture, and ovoid shape. The following factors favor malignant when they are present: stellate infiltrative borders, heterogenous texture, round shape, and presence of coarse calcifications.

In the mammographic image for the patient, a round homogenous lesion is seen. This would favor a benign process. Confirmation of the imaging impression requires histologic examination of the lesion either by biopsy of the lesion or by conservative excision.

Diagnostic Findings, Part 3

The breast nodule is excised and sent for pathologic examination (see Figures 2 and 3).

Questions/Discussion Points, Part 3

What are the Pertinent Histologic Findings Seen in Figures 2 and 3?

On low-power image of the breast biospy, as seen in Figure 2, the lesion is seen to be sharply demarcated from the adjacent normal breast tissue. This is suggestive of a benign process. When looking at higher power in Figure 3, there is a predominance of stromal tissue with compression of the epithelial component. The stroma is of low cellularity with no mitoses or cytologic atypia seen. In addition, the epithelial component shows bland cytologic features with associated myoepithelial cells.

What Is Your Diagnosis?

Fibroadenoma of the breast.

Discuss the Clinical Features and Pathophysiology of Fibroadenomas and What Is the Prognosis and Management for This Lesion?

Fibroadenomas are the most common benign breast neoplasms and typically present in women 20 to 35 years old.[1] The tumors are usually solitary but may be multiple (20%). Clinically, they may be detected by the patient or the physician on breast examination as a well-demarcated, freely mobile, firm mass that is usually <3 cm in diameter. The fibroadenoma is a neoplasm of the specialized lobular stroma with typically low cellularity, no cytologic atypia, and mitotic figures absent or rare. The associated benign epithelium has associated myoepithelial cells and may have an intracanalicular or pericanalicular pattern.[2] The radiographic appearance of fibroadenoma characteristically shows an ovoid homogenous mass with sharp distinct borders.

Patients with fibroadenomas are associated with a slight increased risk of breast cancer, particularly when there are proliferative fibrocystic changes involving the tumor. As would be anticipated, fibroadenomas are hormonally responsive (may enlarge during pregnancy and reduce in size in postmenopause).

As the fibroadenoma is a benign tumor, in the appropriate clinicoradiographic setting, once the tumor is diagnosed by fine-needle aspiration or needle core biopsy, it may be safely followed. If the tumor is a cosmetic problem or if preferred by the patient, conservative excision can be performed.[3]

Discuss a Common Tumor in the Differential Diagnosis of a Fibroadenoma

The histologic differential diagnosis includes the phyllodes tumor in which there is increased cellularity of the stroma, and the epithelial component demonstrates a "leaf-like" architectural pattern.[1] Low-grade phyllodes tumors have these features with mild cytologic atypia and occasional mitoses. High-grade phyllodes tumors in addition to the increased stromal cellularity have marked cytologic atypia and increased mitoses, some of which may be atypical. Because of the higher risk of recurrences, wide excision is indicated for phyllodes tumors. In addition to the risk of recurrences, the high-grade phyllodes tumor has the potential to metastasize.

Teaching Points

- Benign features include the following: Multiple indistinct nodules (lumpy breast) favors fibrocystic changes, and lesions beneath the nipple may suggest a papilloma.
- A fixed irregular firm mass on physical examination is suspicious for malignancy, as is dimpling of the overlying skin.
- On radiography, a benign process tends to have sharp distinct borders, homogenous texture, and ovoid shape.
- Fibroadenomas are the most common benign breast neoplasms and typically present in women 20 to 35 years old.
- The fibroadenoma is a neoplasm of the specialized lobular stroma with typically low cellularity, no cytologic atypia, and mitotic figures absent or rare. The associated benign epithelium has associated myoepithelial cells and may have an intracanalicular or pericanalicular pattern.
- The phyllodes tumor has increased cellularity of the stroma, and the epithelial component demonstrates a "leaf-like" architectural pattern. Low-grade phyllodes tumors may have mild cytologic atypia and occasional mitoses. High-grade phyllodes tumors, in addition to the increased stromal cellularity, have marked cytologic atypia and increased mitoses, some of which may be atypical.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Educational Case: Iron Overload and Hemochromatosis

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, hematopathology, anemia, iron overload, hemochromatosis, genetic mechanisms, inheritance patterns

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Primary Pathology Learning Objective

Objective HRC1.3: Hepcidin Regulation, Iron Overload, and Anemia of Chronic Disease: Discuss the role of hepcidin as an iron regulator and describe how different types of alterations in the hepcidin pathway can produce anemia of chronic disease or iron overload.

Competency 2: Organ System Pathology; Topic HRC: Hematopathology - Red Cell Disorders; Learning Goal 1: Anemia.

Secondary Pathology Learning Objective

Objective GM1.2: Inheritance Patterns: Compare and contrast the inheritance patterns of different types of Mendelian disorders and give examples of each type of pattern.

Competency 1: Disease Mechanisms and Processes; Topic GM: Genetic Mechanisms; Learning Goal 1: Genetic Mechanisms of Developmental and Functional Abnormalities.

Patient Presentation

A 50-year-old Caucasian male presented for evaluation concerned that he may be at risk of developing hemochromatosis based on his family history. His father presented at age 60 with bronzed skin and diabetes; he was found to have iron overload and subsequently has been undergoing therapeutic phlebotomies. The patient's medical history is unremarkable with the exception of hypercholesterolemia, for

Table 1. Iron and Genetic Studies of the Patient and His Father.

Lab Test	Father—Age 60	Patient—Age 50	Normal Range
Serum iron	232	106	65-170 μg/dL
Transferrin	284	230	200-400 mg/dL
Total iron binding capacity	355	288	250-450 mg/dL
% saturation	65	37	20%-55%
Ferritin	1518	217	10-300 ng/mL
HFE genotype C282Y	Homozygous	Heterozygous	

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Table 2. Iron and Genetic Studies of the Father and the Brother of the Patient.

Lab Test	Father—Age 60	Brother—Age 46	Normal Range
Serum iron	232	176	65-170 μg/dL
Transferrin	284	230	200-400 mg/dL
Total iron binding capacity	355	266	250-450 mg/dL
% saturation	65	65	20%-55%
Ferritin	1518	611	10-300 ng/mL
HFE genotype C282Y	Homozygous	Homozygous	

which he takes a statin. You decide to do some diagnostic blood work. In addition, the patient has provided you with results of blood work from his father.

Diagnostic Findings, Part 1

Results of iron studies and *HFE* studies are presented in Table 1.

Questions/Discussion Points, Part 1

Interpret the Father's and the Patient's Iron Studies

The father has elevated serum iron associated with increased transferrin saturation and an elevated ferritin indicative of both increased iron absorption and iron storage. The son has normal iron studies.

Do the Patient's Iron Studies Support the Diagnosis of Hemochromatosis?

No. He does not have evidence of either increased absorption or increased iron stores. Additionally, he is only a carrier of the *HFE* mutation, making it highly unlikely that he has a genetic predisposition to iron overload.

Ferritin and Serum Iron Reflect Different Aspects of an Individual's Iron Metabolism. What Is the Major Difference in the Type of Information Obtained From Each of These?

Ferritin is a measure of long-term iron storage, while serum iron (and transferrin saturation) better reflect daily iron absorption. Interpretation of ferritin testing can be misleading with only a single measurement because it is an acute phase reactant.

Diagnostic Findings, Part 2

After obtaining the results above, the patient consults his brother and recommends that he also undergo testing. Results from his brother, again in comparison to those of his father, are shown in Table 2.

Questions/Discussion Points, Part 2

Does His Brother Have Iron Overload? Why Is His Brother's Ferritin So Much Lower Than His Father's?

Yes, he has evidence of iron overload. He is younger than his father was at the time of his iron studies, and the degree of iron overload is a function of time.

Should Other Siblings Be Tested? What Would Be the Best Approach for Further Molecular Testing? If You Had Had the Opportunity to Evaluate the Father at the First Sign of Potential Iron Overload, What Testing Would You Have Done on Him?

Taking the brother's and father's genotypes together (and assuming the brothers have the same father!), mother must be a carrier, and other children have a 50% chance of being homozygotes also. *HFE* C282Y homozygotes in general will have an increased risk of significant iron overload. However, because there are significant modifiers of iron absorption beyond the *HFE* gene (age, gender, diet, and polymorphisms in other genes affecting iron absorption), not all homozygotes will have iron overload.[1] In this family, however, homozygotes do appear to have an increased risk of iron overload, so they should be identified. Because we know the mutation in this case, targeted mutation analysis for *HFE* C282Y is the only analysis needed.

If you had seen the father early in his course and had had no family history of hemochromatosis, it would be appropriate to do targeted analysis for both the *HFE* C282Y and H63D mutations, and if these were negative, sequence analysis could be used to identify other less common mutant alleles associated with *HFE*.

Which Genes Can Cause Hemochromatosis When Mutated? Describe the Inheritance Patterns Seen

The *HFE* C282Y on chromosome 6p22.2, as present in this case, is the most common mutation seen in classic (type 1 or *HFE*1) hemochromatosis and is associated with autosomal recessive inheritance. This mutation accounts for >80% of hemochromatosis cases.[2,3] Another common mutation in *HFE* (H63D) may be seen as a compound heterozygous (C282Y/H63D) genotype in some patients with hemochromatosis; patients with homozygous H63D rarely have clinically significant iron overload.[2,3] Four additional iron overload disorders labeled hemochromatosis have been identified[2]:

Juvenile hemochromatosis is the term given to clinically similar autosomal recessive diseases caused by mutations in 2 different genes:

*HFE*2A: the hemojuvelin (HJV) gene on chromosome 1q21.

*HFE*2B: the hepcidin (HAMP) gene on chromosome 19q13.

*HFE*3, also autosomal recessive, is caused by a mutation in transferrin receptor 2 gene on chromosome 7q22.
*HFE*4, is autosomal dominant and caused by a mutation in SLC40A1 gene on chromosome 2q32.

Discuss the Pathophysiology of How Iron Overload Occurs in Hemochromatosis

Patients with hemochromatosis have in common low hepcidin levels. Hepcidin normally binds ferroportin in both duodenal enterocytes and reticuloendothelial macrophages, which in turn blocks release of iron from these cells. Thus, hepcidin serves to keep iron from being absorbed from the gut or being released from storage macrophages back into circulation. In the absence of hepcidin, this process is reversed, with increased iron absorption and increased turnover of iron from reticuloendothelial macrophages leading to high levels of both serum ferritin and saturation of transferrin and ultimately to iron deposition in tissues.[3]

Teaching Points

- Iron overload can be suspected from serum iron studies, in particular elevated serum iron and transferrin, and increased transferrin saturation.
- In the absence of a historical explanation for iron overload (such as multiple blood transfusions), patients with iron overload should be investigated for genetic disorders, and in particular for hereditary hemochromatosis.
- If hereditary hemochromatosis is identified, family members should be tested for evidence of iron overload as well.
- Other factors modify the effects of the abnormal gene so that affected family members may vary significantly in their clinical and laboratory presentations.
- The most common form of hereditary hemochromatosis is called type 1 and is due to a mutation in the *HFE* gene. It is inherited as an autosomal recessive.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

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Competency 2: Organ System Pathology

Educational Case Background & Submission Instructions

Background

Becoming a competent physician requires the ability to gain a broad foundation of knowledge, skills, and attitudes essential for independent medical practice. Essential in this is the understanding of the normal and pathological processes of each organ system, the ability to apply disease mechanisms to describe the pathobiology, and the ability to continually improve the diagnostic acumen and optimal treatment decisions through lifelong learning.

The Pathology Competencies for Medical Education (PCME) have detailed learning objectives under each goal that direct medical students and course directors to important facets of each learning goal that can be individually applied by learners. The competencies are divided into three sections—disease mechanisms and processes, organ system pathology, and diagnostic medicine and therapeutic pathology—and allow flexibility for each medical school and learner to apply the learning goals and objectives in a way that can keep the unique design of each curriculum or learning plan. The competencies are purposefully kept broad as they represent the minimum requirements of what pathology course directors across the nation have agreed upon to prepare medical students for entry into any residency program and for the subsequent contemporary practice of medicine.

Educational Cases for the PCME are current, peer-reviewed, and highlight the pathology competencies through fictional (but realistic) learning cases that can easily be adapted to multiple types of educational modalities. Educational Cases reference at least one primary learning objective, but may have one or more secondary learning objective(s). The pathology competencies and learning objectives are clearly indicated in the beginning of each case so that the focus of the educational case is evident. Key elements of the current format include clinical presentation, discussion questions or points, learning points, and references. The clinical presentation may include images or laboratory data for the patient's presentation. The discussion questions or points are questions or statements that promote clinical reasoning followed by detailed explanations of the pathology, medicine, or therapeutics brought up in the discussion point or question. The learning points at the end of the case highlight the main teaching points from the preceding discussion. Thus, the cases demonstrate the application of medical reasoning to clinical scenarios that allow the learner to understand and apply diagnostic principles, incorporating morphologic findings and laboratory values with discussion of the laboratory medicine essentials for accurate diagnosis and treatment. References are included in each case and will allow the reader to review the original sources used to create the learning case or gain additional in-depth information. Thus, the Educational Cases are written in a style that can be easily used or adapted to multiple educational formats, such as small group discussions or flipped classrooms.

Case Submission Guidelines

- Submission Portal: https://mc.manuscriptcentral.com/apc
- Manuscript Type: *Educational Case*
- Key Words:
  - *list "pathology competencies" as first keyword*
  - *list relevant competency, topic, learning goal, and objective keywords, e.g. "disease mechanisms, genetic mechanisms, inheritance patterns"*
  - *other relevant keywords from the case content, e.g. "cystic fibrosis"*
- Abstract: *"None needed"*
- Case Content:
  - Primary (and secondary if applicable) learning objective(s), cited from the PCME (doi: 10.1177/2374289517715040)
    - Example of primary objective formatting:
      Objective GM1.2: Inheritance Patterns. Compare and contrast the inheritance patterns of different types of Mendelian disorders and give examples of each type of pattern.
      Competency 1: Disease Mechanisms and Processes; Topic GM: Genetic Mechanisms; Learning Goal 1: Genetic Mechanisms of Developmental and Functional Abnormalities.
  - Patient Presentation: *Include presentation (History of present illness, past medical history, etc. and physical examination)*
  - Diagnostic Findings: *This can include laboratory findings or histology.*
  - Questions/Discussion Points: *The questions and discussion points should be presented in a logical order to promote clinical reasoning. In addition, you can include additional laboratory data/histologic images in later discussion points. The discussions should thoroughly explain the learning objectives to which the case is applied.*
  - Teaching Points: *These should be covered in your discussion.*
  - References: *Linked to the discussion.*
- Images (if applicable): *All images must be original work or have appropriate approval for publication.*

Accepted Cases

Published Educational Cases receive the same scholarly recognition, citation and merit as other articles published in *Academic Pathology*. Cases accepted for publication will incur an Open Access article processing fee of $500.00 for authors who are faculty and students of APC member departments; $750 for non-members. For more information, contact *Academic Pathology* at journal@apcprods.org or 302-660-4940.

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Educational Case: Primary Osteosarcoma

Aldis H. Petricek, BA[1] and Darren Salmi, MD[1,2]

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, musculoskeletal, bone neoplasia, bone, osteosarcoma, primary bone tumors, malignant bone tumors, osteosarcoma risk factors, osteosarcoma staging, tumor staging

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Primary Objective

Objective MS1.2: Bone-Forming Sarcomas in Children: Describe the most common benign and malignant bone-forming tumors in children and adolescents in terms of clinical presentation, radiologic findings, histologic features, treatment, and prognosis.

Competency 2: Organ System Pathology; Topic: Musculoskeletal System (MS); Learning Goal 1: Bone Neoplasia.

Secondary Objective

Objective SP1.4: Staging: Describe the information that the pathologist obtains from a resected tissue specimen, how this information is reported, how it is combined with clinical information to stage the tumor, and how staging information is used to guide treatment.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic: Surgical Pathology (SP); Learning Goal 1: Role in Diagnosis.

Patient Presentation

A 14-year-old male patient presents to the emergency department with severe pain in his right knee. The pain has been intermittent for the past 10 weeks, appearing and disappearing sporadically. The discomfort has grown more regular in the last week and is now compounded by marked swelling around the knee. Further interview reveals that the patient plays on a youth soccer team, and his knee feels especially painful during practice. His parents attributed the symptoms to "growing pains," as the patient's height and weight have been increasing appropriately for his age, and he has had no known skeletal diseases—nor any serious conditions—prior to onset of the pain.

Diagnostic Findings, Part I

Vital signs are evaluated and found to be normal. No systemic symptoms are noted. Physical examination reveals a large, palpable mass on the anterior aspect of the right proximal tibia. The mass is tender to palpation, but not warm to the touch.

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Question/Discussion Points, Part I

Discuss the Differential Based on the Clinical Presentation

The patient's large and painful tibial mass is nonspecific, and the differential diagnosis remains broad. At one level, we may consider whether this mass is neoplastic or non-neoplastic. If non-neoplastic, diagnoses might include Osgood-Schlatter disease, subacute osteomyelitis, or a reactive soft tissue lesion such as myositis ossificans. If the mass were neoplastic, one would first have to decide whether the neoplasm was benign or malignant and whether it involved the bone, soft tissue, or both.

For a patient of this age, the most likely malignancies of the bone are osteosarcoma and Ewing sarcoma. Chondrosarcoma may be considered alongside the two—though in its most common form, chondrosarcoma typically presents in the axial skeleton of persons above 40 years old. The mass may be a metastatic tumor, secondary to cancer elsewhere in the body, but the patient's age and lack of prior disease make this unlikely as well.

Osteosarcoma is the most probable among these malignancies, comprising over 50% of malignant bone tumors for patients younger than 20 years.[1] Ewing sarcoma is the second most common primary bone malignancy in this age-group, representing over 30% of bone cancers for children and adolescents.[2] Children are the highest risk group for both sarcomas, though neither sarcoma accounts for more than 3% of overall childhood cancers.[2] Osteosarcoma most commonly occurs in children between 13 and 16 years of age, while peak incidence of Ewing sarcoma occurs between 10 and 15 years of age.[2,3] This age dependency may be related to the adolescent growth spurt, especially as osteosarcoma often manifests near the metaphyseal growth plate.[4] In both cases, males are at higher risk than females, though the reason for this is unknown.[4]

Some benign bone tumors are capable of forming palpable masses similar to the one seen in the present patient. These include aneurysmal bone cysts (ABCs) and giant cell tumors. However, as we will see, giant cell tumors are exceedingly rare in children and adolescents.

Taking these considerations into account, the differential diagnosis includes Osgood-Schlatter, subacute osteomyelitis, myositis ossificans, osteosarcoma, Ewing sarcoma, chondrosarcoma, metastatic tumor, giant cell tumor, and ABC. At this stage, the differential is based solely on the clinical presentation. The patient's age, his large tibial mass, and his male sex have been particularly informative. A simple radiograph of the area surrounding the palpable mass, in addition to histologic data, will be important for narrowing the differential diagnosis.

Diagnostic Findings, Part II

The Patient's Radiograph Is Shown in Figure 1. Describe the Findings

Figure 1 shows a simple radiograph of the right distal femur, proximal tibia, and proximal fibula. There is an ill-defined mass in the tibial metaphyseal region expanding into the surrounding soft tissue, with "fluffy" calcification. The mass appears to be a neoplasm, as a Codman triangle—a small, triangle-shaped displacement of the periosteum which occurs as a tumor pushes through the bone cortex—can be seen in the medial cortex at the distal edge of the mass.[5] The Codman triangle is identified by a thin layer of ossification beneath a raised edge of periosteum and is indicative of bone tumors such as osteosarcoma and Ewing sarcoma. As such, non-neoplastic disorders can be eliminated from the differential. To further narrow the diagnosis, a deeper understanding of the possible neoplasms—including their radiology, histology, and epidemiology—may be of use.

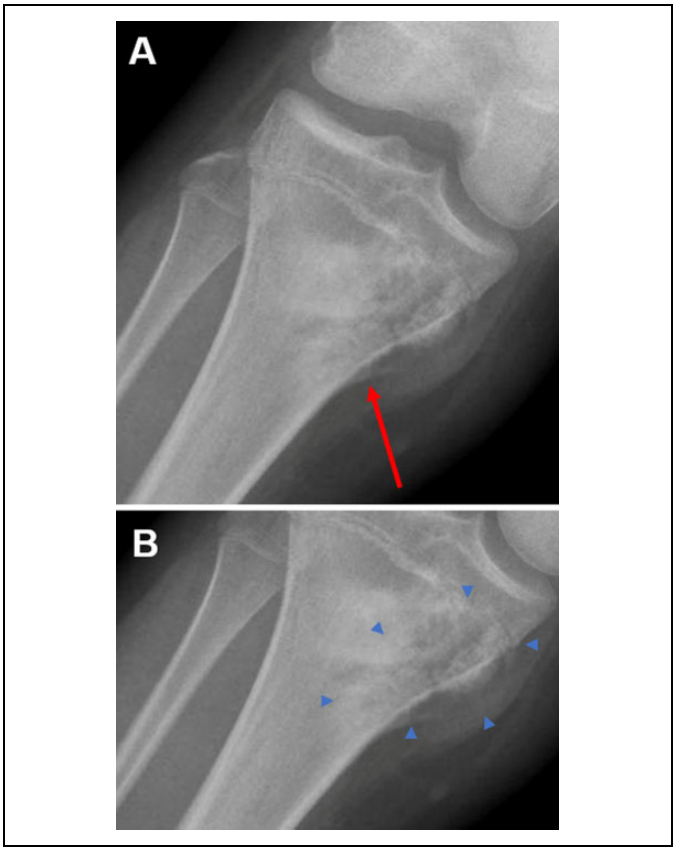

Figure 1. Simple radiograph of the right distal femur, proximal tibia, and proximal fibula. Note the large irregular mass obscuring the proximal tibial metaphysis. Red arrow denotes Codman triangle (A). Blue arrowheads delineate extension of tumor into the surrounding soft tissue (B). The mass is approximately 9 cm at its greatest dimension, according to imaging measurement of a subsequent computed tomography (CT) scan.

Question/Discussion Points, Part II

Describe the Pathological Features, Radiological Characteristics, and Clinical Courses for the Malignant Tumors Under Consideration

At the broadest level, we can delineate between primary and secondary bone tumors. Primary bone tumors originate within

bone cells and do not arise from other cancers. Secondary bone tumors arise from cancers elsewhere in the body and typically arise through metastasis. (This is different from the classification for "secondary osteosarcoma," referenced below.) Depending on the disease and stage, primary malignant bone tumors can have promising outcomes, while secondary bone tumors often carry poor prognoses.

Within the category of primary bone tumors, there exist several malignant and benign variants. Benign tumors are much more common, although malignant bone tumors represent the sixth most common childhood neoplasm and the third most common neoplasm in adolescents and young adults.[6] Approximately 2400 primary bone malignancies are diagnosed in the United States each year.[4]

Osteosarcoma is the most common primary bone malignancy in children and adolescents, representing approximately 400 new cases each year in patients younger than 20 years.[2] The malignancy is a bone-forming tumor with several subtypes, most often producing "woven" osteoid tissue in the metaphyseal regions of the distal femur or proximal tibia.[4] Tumors typically present as painful masses, which may grow larger over time. Patients rarely present with systemic symptoms such as fever or weight loss. Radiographs of osteosarcoma may depict the Codman triangle, which forms as pleomorphic osteoid-producing cells expand through the periosteum.[4] The associated soft tissue mass includes regions of both lytic and sclerotic tissue. Histology shows large, pleomorphic tumor cells with hyperchromatic nuclei and haphazard, lacelike patterns of osteoid and mature bone.[4]

Although osteosarcoma is technically a primary bone tumor, we can further delineate this malignancy into "primary" and "secondary" categories. Primary osteosarcoma is *not* directly related to prior diseases or treatments, while secondary osteosarcoma can develop from prior treatments (eg, irradiation, chemotherapy) or skeletal disorders (eg, Paget disease).[2] Regardless of origin, osteosarcomas are often assumed to have subclinically metastasized by the time a patient is diagnosed.[7] Therefore, treatment often progresses in 3 stages: neoadjuvant chemotherapy, surgical tumor resection, followed by additional chemotherapy and/or radiation. Given timely and proper therapy, two-thirds of patients with nonmetastatic primary osteosarcoma will survive long term.[2]

Ewing sarcoma is the second most common bone neoplasm in children and adolescents, accounting for over 30% of primary malignant bone tumors in this age-group.[2] About four-fifths of Ewing patients are younger than 20 years, and males are slightly more affected than females.[5]

Most often in Ewing sarcoma, primitive round cells develop into large lytic masses, producing tan-white tumors which are often palpable during the physical examination. Nearly 85% of cases involve a balanced translocation, where the $EWSR_1$ gene of chromosome 22 is fused, in-frame, to the FLI_1 gene of chromosome 11.[4] Under radiographic imaging, the resultant lytic masses appear as "moth-eaten" lesions of bone and may elicit the Codman triangle. An associated soft tissue mass may also be seen in radiographs of Ewing patients.[8] Periosteal layers may appear in an "onion peel" fashion, as the periosteum degrades into reactive layers. Histologic data typically reveal consistent groupings of small, round cells with low levels of cytoplasm.[4] In 10% to 20% of Ewing cases, patients may also have systemic symptoms such as fever, malaise, and weight loss.[5] Eighty to ninety percent of Ewing patients will relapse if treated solely with local therapy—suggesting, like osteosarcoma, that many have subclinical metastases at the time of diagnosis.[9] For clinically localized Ewing, treatment therefore involves a neoadjuvant chemotherapy, surgical resection, and adjuvant chemotherapy process similar to that osteosarcoma. When this course is followed, 5-year survival rates for Ewing can reach up to 75%.[4]

Finally, chondrosarcomas are malignant, cartilage-producing tumors, which can also be delineated into smaller categories. The most common category is conventional chondrosarcoma, which accounts for nearly 90% of all chondrosarcomas.[4] The other 10% is divided between dedifferentiated, clear cell, and mesenchymal chondrosarcoma subtypes. Like Ewing and osteosarcoma, the cartilaginous tumors of conventional chondrosarcoma can permeate the medullary cavity, producing large and painful tumors. However, unlike Ewing and most osteosarcomas (which are bone-forming), the tumor is composed of hyaline cartilage. Upon radiographic imaging, such tumors may resemble bright regions of loosely-clumped, irregular calcification. And again in contrast to the other primary bone malignancies, these are typically diagnosed in persons between 40 and 60 years of age.[4] Furthermore, conventional chondrosarcoma is most often found in the axial skeleton, particularly in the pelvic and shoulder regions.[4]

Chondrosarcomas are evaluated by a histologic grading system, which is highly relevant to their pathology and clinical course. This system is organized into 3 categories: grade 1, grade 2, and grade 3. Classifications are made based on the nuclear size, cellularity, mitotic activity, and staining patterns of histological specimens.[4] Grade 1 tumors have low to moderate cellularity; little mitotic activity; and small, round nuclei visible in the chondrocyte cells.[10] These tumors rarely metastasize, with 5-year survival rates near 80%. As a result, treatment may simply involve local resection of the tumor alongside local adjuvant treatment (such as phenolization, cryotherapy, or cementation).[10]

On the other end of the spectrum, grade 3 chondrosarcomas are highly cellular, with extreme nuclear pleomorphism and remarkable mitotic activity. In contrast to grade 1 tumors—which contain abundant hyaline cartilage—grade 3 tumors have sparse levels of chondroid matrix.[4,10] The 5-year survival rate for patients with grade 3 chondrosarcoma is only 43%, and surgical resection is rarely sufficient to prevent relapse.[4] Regardless, chondrosarcoma is an unlikely diagnosis given the patient's age and tumor localization.

Discuss the Benign Tumors Mentioned in the Differential

In theory, both giant cell tumor and ABC could produce a palpable mass like the one seen in this patient. And though the

patient is not likely suffering from either form of tumor, the possibility merits consideration.

Giant cell tumors are aggressive collections of multinucleated, osteoclast-like cells.[4] Osteoclasts—which break down and reabsorb bone tissue—are normally quite active and multinucleated. But in giant cell tumors, these cells expand through and degrade the overlying bony cortex, producing a large mass of soft tissue. These osteoclast-like cells can contain over 100 nuclei each and are interwoven with groups of smaller, uniform mononuclear cells.[4] Their resultant tumors are soft and covered by a thin layer of reactive bone, with little bone tissue inside. In simple radiographs, they appear as expansive and lytic masses which are destructive to the bone cortex. These tumors are highly variable in their clinical behavior, though most are found in the distal femur or proximal tibia, and can be resected through curettage. Although the size and location of this patient's tibial mass correspond to those of giant cell tumors, such tumors are exceedingly rare in children and adolescents. Therefore, the patient is not likely suffering from a giant cell tumor.

Aneurysmal bone cysts most often present in the metaphysis of the long bones in patients younger than 20 years.[4] These tumors are actually blood-filled cystic bodies, surrounded by fibrous walls which contain osteoblasts, osteoclasts, and woven bone tissue. The cysts are expansive and can rapidly degrade bone tissue, while also eliciting painful swelling. Radiographically, they appear as circumscribed "soap bubbles" or "egg shells," with thin sclerotic rims surrounding the lesion, and fluid levels indicative of blood within the cystic space. Excision or curettage are the most effective treatments, though cysts can still recur afterward. Given this patient's age, alongside his tumor location and size, one might be inclined toward a diagnosis of ABC. However, the typical ABC—with its "egg shell" appearance and high fluid levels under radiographic imaging—contrasts starkly with the mass seen in Figure 1. As such, the patient is not likely suffering from an ABC, reaffirming the likelihood of a malignant neoplasm.

Might This Patient Have a Secondary (Metastatic) Bone Tumor?

Secondary bone tumors carry very poor prognoses, yet are much more common than primary bone tumors.[4] However, the patient is not likely suffering from a secondary tumor. Firstly, because metastatic bone tumors rarely occur in the tibia—a majority occur in the axial skeleton, especially in the vertebral column.[4] (The patient has no indication of neoplasia in the axial skeleton, though a full-body positron emission tomography [PET] scan would be necessary to rule this out.) Secondly, most secondary bone tumors have metastasized from a few characteristic neoplasms. In adults, these are malignancies of the breast, lungs, thyroid, kidneys, and prostate; in children, they are neuroblastoma, Wilms tumor, and rhabdomyosarcoma.[4] Because the patient has not suffered from any malignancy prior to the clinical presentation, he is very unlikely to have a secondary bone tumor. (It is important to note the difference between secondary *bone tumors* and secondary *osteosarcoma*, mentioned above.) Nonetheless, a full-body PET scan could be used to identify possible primary cancers elsewhere in the body.

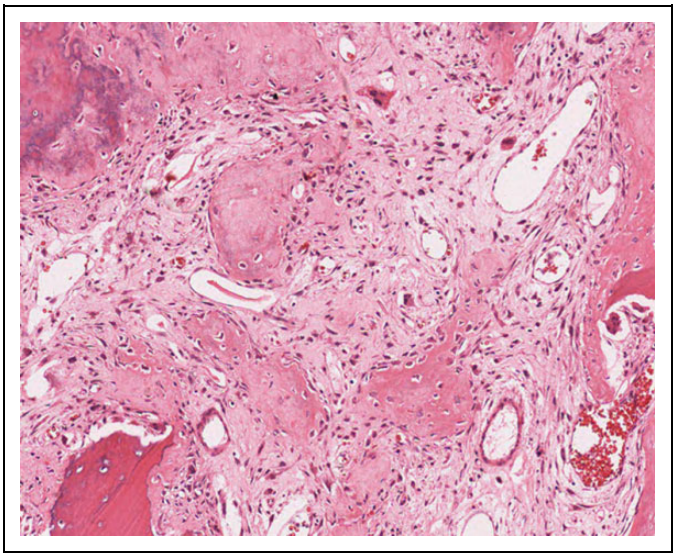

Figure 2. Histological slide from core needle biopsy of the right proximal tibia. Note the woven, haphazard arrangement of osteoid tissue and immature bone. Bottom left-hand corner shows region of darker, matured lamellar bone. Upper left-hand corner shows region of immature, ossifying tissue, more organized than surrounding light-pink osteoid material. Magnification = ×80.

What Further Testing Is Indicated for This Patient?

Histological data are necessary to form an accurate diagnosis. These data could be acquired through either an open biopsy or a core needle biopsy. A full-body PET scan should also be ordered to rule out metastases and to confirm that the bone tumor is not secondary to another cancer elsewhere in the body.

Diagnostic Findings, Part III

The PET Scan Reveals No Clinical Metastases. A Core Needle Biopsy Is Performed, Yielding the Histological Specimen of Figure 2. Describe the Findings, and How They Influence Your Diagnosis

The histological image shows spindle-like, pleomorphic bone-forming cells, characteristic of a malignant neoplasm. Loosely woven pink osteoid tissue occupies most of the image, suggesting that these are osteoid-producing cells. (One can tell osteoid tissue from normal bone, by identifying the lighter, less-organized immature proteinaceous material.) In the bottom left-hand corner, darker, solid red tissue indicates more mature bone. This can be seen from the apparent mineralization (leading to darker appearance) and characteristic lamellae. Early ossification is occurring in the upper left-hand corner, shown by the moderately darkened and partially mineralized tissue.

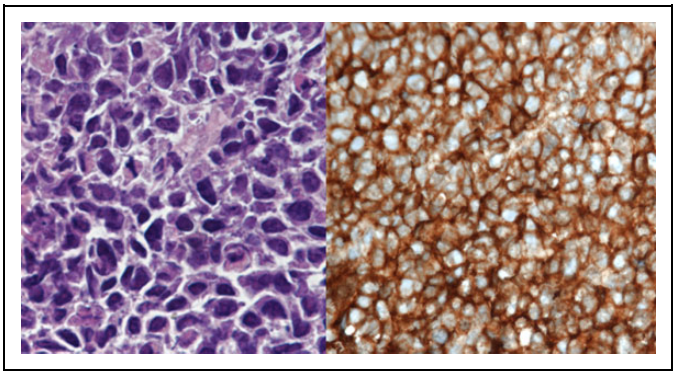

Figure 3. Histological slide typical of Ewing Sarcoma (left) and Ewing Sarcoma under CD99 immunohistochemical staining (right). Note the monotonous presence of immature small round cells, as well as the high nucleus to cytoplasm ratio. Magnifications = ×400.

As a whole, the image shows haphazard arrangements of mature and immature bony material. Clearly, this is a malignant sarcoma which has been producing irregular osteoid tissue. In combination with the radiograph from Figure 1, this is likely an osteosarcoma. Given that this patient has no other clinically notable tumors, the osteosarcoma is a primary neoplasm.

Question/Discussion Points, Part III

What Would You Have Expected to See If This Were an Ewing Sarcoma?

If this patient had Ewing, one would *not* expect to see pleomorphic cells surrounded by irregular osteoid tissue. Instead, one would expect consistent groupings of small round cells, each about the size of a lymphocyte.[5] These cells would have a very high nucleus to cytoplasm ratio, with minimal sign of stroma, giving a characteristically dark stain to the resulting image. Figure 3 provides an example of this. Additionally, Ewing sarcoma cells are positive for CD99 by immunohistochemical staining, because their cell surfaces contain the CD99 antigen which is bound by the stain.

Even Though Osteosarcoma Is the Most Common Childhood Malignant Bone Neoplasm, It Still Accounts for Just 3% of Childhood Cancers. What Risk Factors Might Have Predisposed This Patient to the Disease?

Before delving into specific risk factors, one might revisit the difference between primary and secondary osteosarcoma. Primary osteosarcoma, like other primary bone tumors, originates in bone cells and is not directly associated with another cancer or disease. Secondary osteosarcoma also originates in bone cells but is associated with either a skeletal disease or treatment from another condition (typically cancer). Perhaps confusingly, both forms are considered "primary bone tumors," because both arise from bone cells themselves. Nonetheless, primary osteosarcoma is the predominant form in children and adolescents.

Genetic predisposition likely plays a role in childhood primary osteosarcoma. For example, approximately 70% of sporadic osteosarcoma tumors contain acquired mutations in *RB*, the negative cell cycle regulator.[4] Most commonly, these are loss-of-heterozygosity mutations, though point mutations also contribute.[11] Germline *RB* mutations also play a role, increasing osteosarcoma risk 1000-fold.[4]

Inactivation of *TP53*, which codes for a protein critical to apoptosis and DNA repair, has also been linked to osteosarcoma.[2,4,12] For instance, patients with Li-Fraumeni syndrome (characterized by germ line inactivation of *TP53*) can suffer from osteosarcoma in addition to a multitude of other cancers. Inactivation of the *$CDKN_2A$* gene—which codes for p14 and p16, 2 proteins involved in tumor suppression—also increases risk for osteosarcoma. This occurs through 2 respective pathways: those of p53 and Rb, respectively.[11] With the former, p14 functions to inhibit degradation of p53 (the product of *TP53*) by sequestering the E3 ubiquitin ligase to the nucleolus, thereby preventing ubiquitin tagging of p53. In the latter, p16 acts as negative regulator of CDK4, which typically phosphorylates Rb (the product of *RB*). When CDK4 does phosphorylate Rb, the cell cycle is allowed to progress from G_1 to S phase; inactivation of p16, therefore, keeps this checkpoint constitutively open.[11,12] (It is important to note that loss-of-function mutations in *RB*, referenced above, can remove this checkpoint entirely.)

Unlike Ewing sarcoma, there is no characteristic translocation—or any canonical genetic mutation—associated with osteosarcoma.[4,11] However, the latter neoplasia has recently been linked to chromosomal instability (CIN), a heterogenous, genome-wide set of chromosomal alterations, which impacts the number of chromosomes or sections within chromosomes.[11] In turn, CIN itself arises from dysfunction in the cell cycle and DNA repair processes, partially explaining the importance of genes such as *RB* and *TP53* in osteosarcoma.

As noted, a host of chromosomal alterations play a role in CIN-related osteosarcoma. For instance, chromosomes 3, 6, 9, 10, 13, 17, and 18 contain common locations for deletion events which impact copy number variation in osteosarcoma cells.[1] These regions are notable for encoding numerous tumor suppressors, explaining why such deletions may increase risk for osteosarcoma.[11,12] On the other hand, chromosomes 1, 6, 7, and 17 contain notable oncogenes and are the most common sites for amplification in osteosarcoma-related copy number alterations.[12] These complex rearrangements have potential for widespread genetic variations, even between osteosarcoma cells. As a result, the genetic etiology of osteosarcoma remains unknown, and the search for targeted molecular treatments remains unsuccessful.[11,12]

Prior irradiation—from an earlier primary cancer, for instance—increases risk for secondary osteosarcoma and may be responsible for approximately 3% of osteosarcomas.[2] Exposure to chemotherapy heightens this effect.[2] The incidence of irradiation- and chemotherapy-related secondary osteosarcoma

may only increase with time, as survival rates rise for certain childhood cancers.

Because 75% of osteosarcoma cases occur in persons younger than 20 years, much attention is paid to the risk factors for children and adolescents.[4] But in truth, osteosarcoma displays a bimodal age distribution, with older adults comprising a smaller, yet still significant proportion of cases. Interestingly, adult patients are more likely to develop osteosarcoma in the axial skeleton, and patients over 60 years old are at highest risk for metastatic tumors. In contrast to their younger cohorts, these patients often suffer from *secondary* osteosarcoma, typically associated with Paget disease. Paget, notable for its accelerated and disordered pattern of bone turnover, occurs in 1% of US adults older than 40 years.[4] Just fewer than 1% of Paget patients will undergo sarcomatous transformation of the disease, leading to secondary osteosarcoma.[2] In polyostotic cases of Paget (ie, cases involving multiple bones), this figure increases to 5% to 10%.[4]

Now That You Have Diagnosed the Patient With Primary Osteosarcoma, How Do You Stage the Cancer?

Bone sarcoma staging guidelines, set by the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control, operate using the TNM staging system.[2,13] In this system, tumors are evaluated for their size and extent (T), lymph node involvement (N), and metastases (M). There is also a category for histological grade (G). Each category contains a set of grades, depending on the type of tumor (eg, bone sarcomas). For instance, bone sarcomas in the appendicular skeleton have 5 grades for tumor extent: TX (primary tumor not assessable), T0 (no evidence of primary tumor), T1 (tumor $\leq$8 cm at greatest dimension), T2 (tumor $\leq$8 cm at greatest dimension), and T3 (discontinuous tumors in the primary bone site). Tumors are also evaluated for their absence (N0) or presence (N1) of regional lymph node metastases, alongside their absence (M0) or presence (M1) of distant metastases. If distant tumors have metastasized to the lung, they are classified at M1a, while metastases to the bone or other distant sites are classified as M1b. Finally, histological specimens are considered well differentiated and low grade (G1), moderately differentiated and high grade (G2), or poorly differentiated and high grade (G3). Finally, the AJCC provides a framework for assigning an overall "stage group" based on these collective classifications.[13]

According to imaging analysis, the patient's tumor is approximately 9 cm at its greatest dimension (Figure 1), making it a T2 bone sarcoma. The full-body PET scan revealed no metastases, qualifying as both N0 and M0. Finally, the histology appears to be moderately differentiated, indicating a G2 grade. Taken together, these classifications place the tumor in the II-A stage group. One should note that the tumor has been staged using "clinical staging" practices, which do not include surgical measurement. A "pathological stage" could be reached by incorporating data from surgical exploration or from removal of the tumor. These pathological data do, at times, alter the conclusions of clinical staging.

The Musculoskeletal Tumor Society (MSTS) provides separate staging guidelines for bone sarcomas.[14] The MSTS guidelines categorize malignant bone tumors by grade: stage I (low grade), stage II (high grade), and stage III (tumors with distant metastases). Within each stage, tumors are characterized as type A tumors (intracompartmental, contained within the bone cortex) and type B (extracompartmental, extending beyond the cortex). The final stage is used for surgical decision-making, with no impact on chemotherapeutic approach.

Given the lack of clinically notable metastases, this tumor is either stage I or stage II. The tumor is large, and histology shows a marked proliferation of osteoid cells, suggesting that this is a high-grade stage II tumor. Furthermore, the tumor has clearly lifted the periosteum (demonstrated by the Codman triangle) and expanded into the surrounding soft tissue. The patient can therefore be diagnosed with a stage II-B primary osteosarcoma when regarding the MSTS guidelines.

Briefly Describe the Therapeutic Approaches for This Patient

As noted, the treatment of primary osteosarcoma typically involves 3 stages: neoadjuvant chemotherapy, surgical resection of the tumor, and adjuvant chemotherapy. In the absence of clinically detected metastases, 5-year survival rates range between 60% and 70%.[2,4] When chemotherapy is excluded, however, up to 80% of patients will develop metastatic tumors (even if the original cancer is locally controlled).[2] This patient should, therefore, follow the standard 3-stage protocol.

There is no consensus on the ideal chemotherapy for bone sarcomas. Nonetheless, the American Osteosarcoma Study Group (AOST) has put forth the MAP regimen, which uses methotrexate, doxorubicin, and cisplatin for both neoadjuvant and adjuvant therapy.[15] In the AOST protocol, the neoadjuvant phase lasts for 10 weeks, surgery is performed in week 11, and adjuvant therapy resumes for weeks 12 through 29. A leucovorin rescue can be used alongside high-dose methotrexate.

Between the neoadjuvant and adjuvant chemotherapy, there are 2 main surgical approaches. The first is amputation of the affected region; the second is limb-sparing resection of the tumor. (With tumors of the metaphyseal region, resection is typically "osteoarticular," removing the tumor, the tumor-bearing bony portion, and portions of the adjacent joint.)[16] Oncologic outcome is of primary concern when choosing a surgical approach, and functional outcomes are secondary. If complete excision of the tumor is anatomically impossible, or otherwise complicated, amputation remains the "gold standard" to avoid recurrence and metastasis.[16] Nonetheless, the use of limb-sparing resections has increased with the employment of effective chemotherapy. And regardless of approach, the level of chemotherapy-induced tumor necrosis found during surgery is highly relevant to long-term prognosis.[4,16]

Given this patient's age, activity level, and lack of clinical metastases, limb-sparing surgery is preferable to amputation. However, the patient will likely require reconstructive surgery. An allograft or expandable endoprosthesis may be suitable for his immature skeleton, allowing for equal development of his lower limbs.

If initial treatment is deemed successful, the National Comprehensive Cancer Network recommends follow-up surveillance every 3 months for years 1 to 2, every 4 months during year 3, every 6 months for years 4 to 5, and once annually from year 6 onwards.[15] While there is no established time line for the duration of follow-up, most bone sarcoma recurrences occur within 10 years of treatment.[15]

Teaching Points

- Radiographs of osteosarcoma typically depict a soft tissue mass, including lytic and sclerotic tissue, alongside the notable Codman triangle.
- Bone tumors can be classified as primary (originating in the bone itself) or secondary (having metastasized from elsewhere in the body).
- Osteosarcoma and Ewing sarcoma are the most common primary malignant bone tumors in children and adolescents.
- Osteosarcomas are malignant bone-forming tumors which produce woven osteoid tissue and comprise 50% of all childhood bone neoplasms.
- Histology of osteosarcoma shows haphazard arrangements of loosely woven osteoid tissue, surrounded by sections of mature lamellar bone.
- While there is no established genetic etiology of osteosarcoma, CIN is common among osteosarcoma cells.
- Giant cell tumors are soft, benign collections of multinucleated osteoclast-like cells, which appear near the epiphysis of the long bones.
- Aneurysmal bone cysts are benign, blood-filled cystic bodies which typically appear as "egg shell" masses near the metaphysis of the long bones.
- Malignant bone tumors are staged after diagnosis and before treatment. The specific stage of any given tumor will influence the prognosis and treatment of that cancer.
- In the AJCC guidelines, bone sarcomas are evaluated for tumor extent (T), lymph node involvement (N), distant metastases (M), and histologic grade (G). They are then given an overall "stage group" (stages I-IV, subgroups A-B) based on these evaluations.
- In the MSTS guidelines, bone sarcomas are staged by their grade (stages I-III) and whether they are intracompartmental (A) or extracompartmental (B).
- Clinical staging of a tumor can be reached through imaging or other nonsurgical measurements, while pathological staging requires surgical exploration or removal of the tumor.
- Treatment for osteosarcoma typically involves neoadjuvant chemotherapy, surgical removal of the tumor, and adjuvant chemotherapy.
- Chemotherapy of osteosarcoma often follows the MAP regimen—methotrexate, doxorubicin, cisplatin—for both neoadjuvant and adjuvant phases.

Declaration of Conflicting Interests

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Educational Case: Wilms Tumor (Nephroblastoma)

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, kidney, renal neoplasia, Wilms tumor, nephroblastoma, abdominal mass, pediatric tumors

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Primary Objective

Objective UTK1.4: Wilms Tumor: Describe the clinical and pathologic features and molecular basis for Wilms tumor and list the histologic features that are important to recognize in determining prognosis, and the etiology of Wilms tumor as part of different syndromes.

Competency 2: Organ System Pathology; Topic UTK: Kidney; Learning Goal 1: Renal Neoplasia.

Patient Presentation

A 3-year-old male presents to the clinic with his mother who has noticed a rapidly growing mass in the left side of his abdomen. She has also noticed a pink tinge to his urine and noted that he often cries with urination. On physical examination, the physician palpated a large left-sided abdominal mass with smooth, regular margins that did not cross the midline. The rest of the physical examination was unremarkable. Ultrasound and contrast-enhanced computed tomography (CT) scans of the abdomen were ordered.

Questions/Discussion Points, Part 1

What Is the Differential Diagnosis for an Abdominal Mass in a Young Child?

The differential diagnosis for an abdominal mass in a young child consists of disorders of renal origin (neoplastic, nonneoplastic), cysts of other abdominal organs (mesenteric, omental, choledochal), other neoplasms (neuroblastoma, teratoma, hepatoblastoma), or congenital (developmental) abnormalities.[1]

Diagnostic Findings, Part 2

Imaging

Ultrasound revealed an 8 × 7 cm well-defined mass of heterogeneous echogenicity arising from the left kidney. Heterogeneity is due to hemorrhage and necrosis. On CT scan, a large mass with low-density areas signifying tumor necrosis was seen. There was no evidence of nodal or hepatic metastasis. The right kidney was unremarkable.

Pathologic Examination

The left kidney was resected (Figure 1). On gross examination, a lobulated tan mass with surrounding pseudocapsule is visualized arising from the left kidney. It appears as a heterogenous

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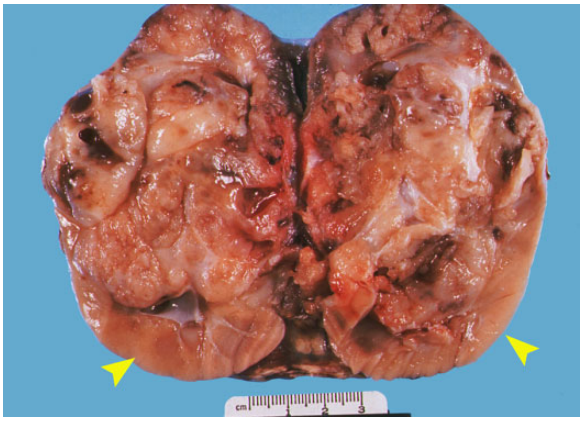

Figure 1. Kidney sectioned in half showing a hemorrhagic tan-white 8 × 7 cm necrotic mass compressing the non-neoplastic renal parenchyma (arrowheads).

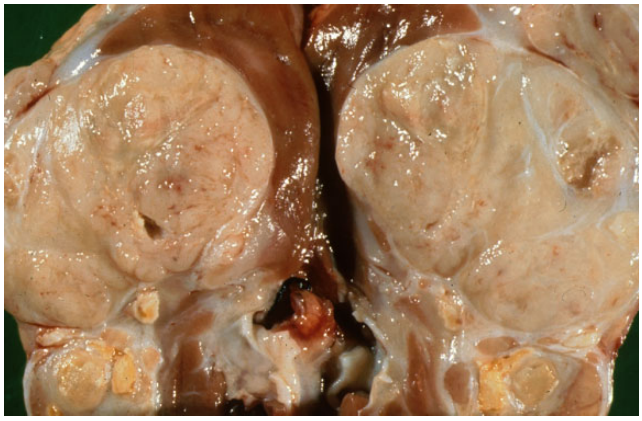

Figure 3. The bisected kidney demonstrates a large, tan-white, bulging, well-demarcated tumor compressing the normal renal parenchyma.

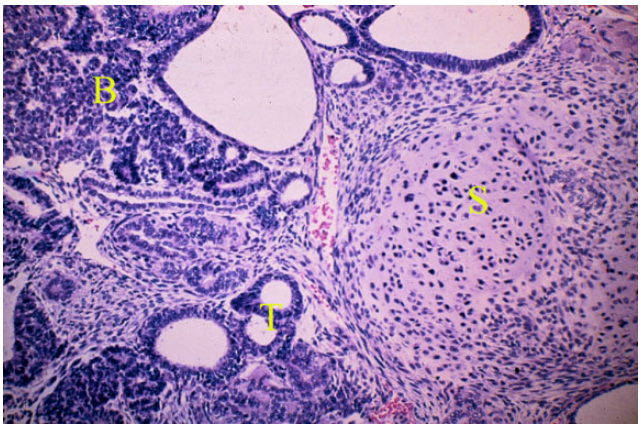

Figure 2. Triphasic tumor composed of blastema (B), epithelial elements (tubules) (T), and stroma (S). H&E, Intermediate power.

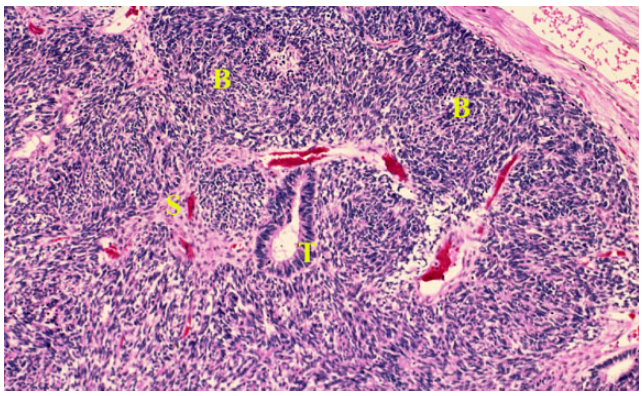

Figure 4. Blastema-predominant Wilms tumor composed of small round blue cells (B) intermixed with single tubule (T) and stromal elements (S). H&E, Intermediate power.

mass with prominent foci of necrosis and hemorrhage. Tissue submitted for histological examination demonstrates a mixed pattern of blastemal, stromal, and epithelial elements (Figure 2).

Questions/Discussion Points, Part 2

What Is the Diagnosis Based on the Clinical, Imaging, Gross and Histological Findings?

The clinical (left-sided abdominal mass), imaging (8 × 7 cm heterogenous echogenic mass on ultrasonography), gross (lobulated tan heterogenous mass), and histological findings (mixed pattern of blastemal, stromal, and epithelial elements) are consistent with a diagnosis of Wilms tumor (WT; nephroblastoma).

Describe the Gross and Microscopic Pathologic Features of Nephroblastoma

Grossly, the mass may appear as a large, bulging, tan-white lobulated, homogenous mass that is sharply demarcated from the renal parenchyma (Figure 3) or as a heterogeneous mass with necrosis and hemorrhage, as in this case (Figure 1).[2] Wilms tumor typically occurs unilaterally, but in 5% to 10% of cases the malignancy appears bilaterally, either simultaneously or one after the other. Microscopically, the classic WT is a combination of blastemal, stromal, and epithelial elements (mixed tumor; Figure 2). Neoplasms containing all elements are commonly referred to as triphasic tumors. When one component consists of more than two-thirds of a tumor, the term monophasic tumor is used. The triphasic tumor is the most frequent pattern followed by the blastema-predominant pattern (Figure 4). Blastemal cells are the least differentiated and consist of primitive small round blue cells. The epithelial component ranges from primitive rosette-like structures to tubules or glomerular-like structures. The stromal component appears as densely packed undifferentiated mesenchymal cells interspersed with loose cellular myxoid regions or contain heterologous elements (skeletal muscle, cartilage, and bone).[3]

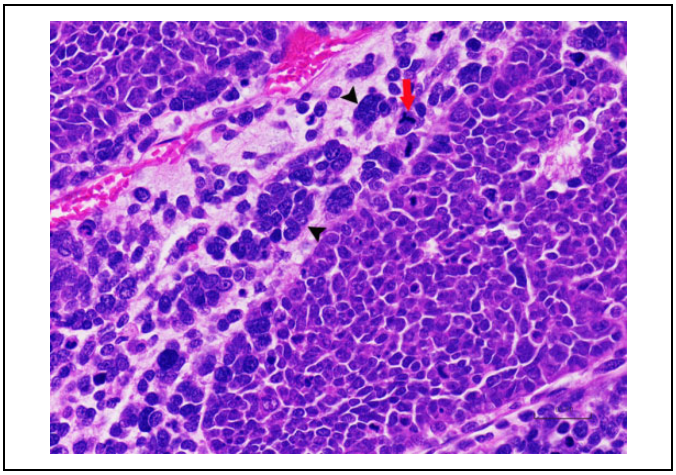

Figure 5. The large hyperchromatic cells (arrowheads) and atypical mitotic figure (red arrow) are demonstrative of anaplasia in a nephroblastoma. H&E, Intermediate power.

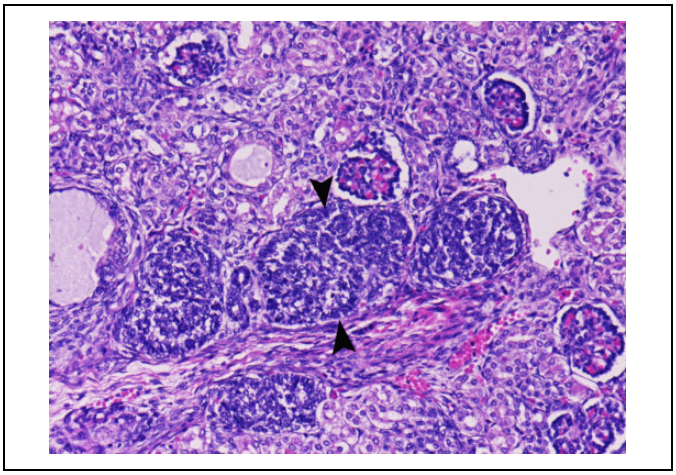

Figure 6. Nephrogenic rest. Persistent foci of embryonic cells (arrowheads) are present within the renal parenchyma. H&E, Intermediate power.

What Histological Finding Is Classified as Unfavorable Histology?

The presence of diffuse anaplastic histology, observed in approximately 5% of WTs, would correlate with a poor prognosis. Three features define anaplasia: prominent cytologic atypia (nuclear diameter greater than 3 times the size of the adjacent nuclei), hyperchromasia, and atypical mitotic figures (Figure 5). Anaplasia classified as "unfavorable histology" correlates with TP53 mutations and resistance to chemotherapy.[4]

What Is the Epidemiology of Wilms Tumor in the United States?

Wilms tumor has an incidence of 1 in 10 000 children in the United States.[4,5] It is the most prevalent primary renal tumor and the most common intra-abdominal solid tumor of childhood. Wilms tumor is the fourth most common malignancy in the pediatric population in the United States. Peak incidence is between ages 2 and 4 with 80% of cases presenting before age 5.[6]

Describe the Molecular and Developmental Abnormalities Associated With Wilms Tumor

Both inherited and sporadic forms of WT can arise. Mutation involving inactivation of the WT1 tumor suppressor gene locus on chromosome 11p13 often is a predisposing factor. Wilms tumor 1 protein normally functions as a transcriptional activator of genes that are involved in differentiation of renal and gonadal cells. It is a primary regulatory component during kidney development that governs the transition from mesenchymal cells to epithelial cells.[7]

Define "Nephrogenic Rests"

Nephrogenic rests (NRs) are abnormal areas of embryonic tissue that persist beyond 36 weeks of development and may be either perilobar or intralobar and are thought to be a precursor lesion for WT (Figure 6).[3,4] Nephrogenic rests are observed in approximately 25% to 40% of unilateral WT cases and 100% of bilateral WT cases. Perilobar NRs occur peripheral to the renal lobules and have been associated with the Beckwith-Wiedemann syndrome. Intralobar NRs are found within the central part of the lobule and have been associated with WAGR and Deny-Drash syndromes.[8]

What Syndromes Are Associated With Wilms Tumor?

Wilms tumors associated with syndromes account for approximately 10% of all cases.[4] WAGR syndrome is one such syndrome consisting of WT, aniridia, genital anomalies (cryptorchidism, hypospadias, etc), and mental retardation.[4,6] Approximately one-third of individuals with WAGR syndrome will develop WT over the course of their lifetime. This syndrome is characterized by germline deletion of chromosome 11p13 which carries the WT1 and PAX6 genes coding for WT and aniridia, respectively. Another syndrome increasing the risk of developing WT is Denys-Drash syndrome consisting of pseudohermaphroditism and progressive glomerulonephritis leading to renal failure. This syndrome is caused by altered DNA-binding properties of the zinc finger region of the WT1 protein due to a dominant negative missense mutation. Wilms tumor is seen in these patients only when there is biallelic inactivation of WT1. Beckwith-Wiedemann syndrome is another instance of increased risk of development of WT and occurs due to loss of function of the WT2 gene on chromosome 11p15. This syndrome is characterized by macroglossia, omphalocele, organomegaly, genitourinary anomalies, and increased risk of abdominal tumors. Genes present in the 11p15.5 region are normally subjected to imprinting, so only one of the 2 parental alleles are expressed. The phenotype and predisposition to tumorigenesis are specific to the type of imprinting abnormality that is seen in the affected individual. The insulin-like growth factor-2 gene expression has the

greatest correlation with tumor predisposition in Beckwith-Wiedemann syndrome.

What Other Neoplasms Are in the Differential?

Other renal tumors include congenital mesoblastic nephroma, clear-cell sarcoma, and rhabdoid tumor.[5,7] Other small round blue cell tumors of childhood that should be considered include neuroblastoma and primitive neuroectodermal tumor. Hepatoblastoma is another malignancy in the differential. Differential diagnosis is based on clinical and imaging findings. Diagnosis is based on pathologic features.

What Are Therapeutic Options After Diagnosis of Wilms Tumor?

Most patients can be cured of WT. Tumor staging is a surgical and pathological designation; most commonly the North American National Wilms Tumor Study Group staging system is used. In the United States, surgical resection is the first step in treatment and staging and will be followed by chemotherapy and radiotherapy if indicated.[7] Protocol in other countries involves primary treatment with chemotherapy to decrease the risk of intraoperative rupture and hemorrhage and to reduce the disease stage at the time of surgical resection. Stage I disease is limited to the kidney with the capsule intact and can be removed completely. Stage II disease indicates tumor has extended locally beyond the kidney capsule but is completely excised. Stage III WT is designated for tumors that cannot be completely excised. After surgery, there is residual nonhematogenous tumor that may include positive hilar or periaortic lymph nodes or positive margins at location of excision. Stage III also includes suspected peritoneal contamination following tumor rupture or surgical biopsy. Presence of distant tumor deposits such as lung, liver, or bone involvement qualifies as stage IV disease. Stage V WT is defined as bilateral renal tumors at the time of diagnosis. Each tumor is staged separately.[9]

Teaching Points

- An unidentified mass in an infant can be of renal (55%), gastrointestinal (15%), pelvic (15%), adrenal (10%), or hepatobiliary (5%) origin.
- Wilms tumor is the most common renal malignancy in children with an incidence of 1 in every 10 000 children.
- Wilms tumor is primarily a sporadic disease, but it can be associated with several congenital syndromes including WAGR syndrome, Denys-Drash syndrome, and Beckwith-Wiedemann syndrome.
- Diagnosis of WT requires histological confirmation, and staging is determined by the anatomic extent of the tumor.
- Therapeutic options at presentation, based on stage, consist primarily of surgical resection followed by adjuvant chemotherapy or radiation therapy in patients with more advanced disease.
- Diffuse anaplasia is an adverse prognostic feature in WT.

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Educational Case: Membranous Nephropathy

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, kidney, glomerular disorder, nephrotic syndrome, nephritic syndrome, membranous nephropathy

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Primary Objective

Objective UTK5.2: Nephrotic Syndrome. Describe the pathophysiology and morphologic features of nephrotic syndrome and contrast with nephritic syndrome.

Competency 2: Organ System Pathology; Topic UTK: Kidney; Learning Goal 5: Renal Syndromes.

Patient Presentation

A 48-year-old Caucasian male with no previous medical history presented to his family physician complaining of widespread swelling, notably around his eyes and upper and lower extremities. He stated the swelling began 2 months ago and complained his urine had a foamy appearance. He denied fatigue, fever, chills, cough, shortness of breath, chest pain, abdominal pain, nausea, vomiting, diarrhea, constipation, hematuria, and rashes/skin lesions. He denied taking any medications. He did not have a history of diabetes, hypertension, heart disease, liver disease, or cancer. He denied using tobacco products or illicit drugs but had consumed alcohol on occasion (1-2 drinks, 1-2 times per month).

Diagnostic Findings, Part 1

On physical examination, vital signs showed a temperature of 98°F, a heart rate of 82 beats per minute, a respiratory rate of 16 breaths per minute, and a blood pressure of 128/84 mm Hg. Physical examination showed a well-appearing male with bilateral periorbital edema, 1+ pitting edema two-thirds of the way from the wrists to the elbows bilaterally with moderately edematous hands and wrists, and 2+ pitting edema to the knees bilaterally with markedly edematous feet and ankles. There was shifting dullness on percussion of the posterior thorax. The remainder of the examination was unremarkable.

Questions/Discussion Points, Part 1

What Is the Differential Diagnosis Based on the History and Physical Examination?

The differential diagnosis of generalized edema includes a glomerulopathy, heart failure, liver disease, myxedema, lymphatic obstruction, and medications. Given the patient's urinary complaint, the glomerulopathies were given particular consideration.

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Diagnostic Findings, Part 2

Laboratory Studies

An extensive laboratory workup including a complete blood count, comprehensive metabolic panel, prothrombin time, lipid profile, thyroid profile, urinalysis, and electrocardiogram was conducted. The complete blood count, prothrombin time, thyroid profile, and electrocardiogram were within reference ranges. The comprehensive metabolic panel showed a serum albumin of 1.8 g/dL. The lipid profile showed total cholesterol of 324 mg/dL and triglycerides of 300 mg/dL. The urinalysis showed significant proteinuria (4+).

The findings prompted the following laboratory workup to determine etiology. An antinuclear antibody test, serum C3 and C4 complement levels, hepatitis B and C and HIV serologies, and a 24-hour urine collection were ordered. The antinuclear antibody test, serum C3 and C4 complement levels, and hepatitis B and C and HIV serologies were within reference ranges. The 24-hour urine collection showed 5.5 g/d of protein.

Imaging

Standard erect and lateral decubitus chest radiographs were ordered. The lateral film showed a 3-mm-thick fluid layer (approximately 60 mL of fluid). The posteroanterior film was unremarkable.

Questions/Discussion Points, Part 2

What Is the Differential Diagnosis Based on the Laboratory Findings?

The tetrad of edema, proteinuria, hypoalbuminemia, and hyperlipidemia define the nephrotic syndrome, which may be caused by a primary glomerular disease or be secondary to a systemic disease such as diabetes mellitus, systemic lupus erythematous, amyloidosis, or certain infections (hepatitis B and C and HIV) or malignancies.[1,2] As the patient's glucose level, antinuclear antibody test, serum C3 and C4 complement levels, prothrombin time, thyroid profile, and hepatitis B and C and HIV serologies were within reference ranges and his history was negative for malignancy, all secondary causes from the differential diagnosis were eliminated. The primary causes of nephrotic syndrome—membranous nephropathy, minimal change disease, focal segmental glomerulosclerosis, and membranoproliferative glomerulonephritis—were still considered.

What Is the Pathogenesis of Nephrotic Syndrome and How Does It Differ From That of Nephritic Syndrome?

The nephrotic syndrome is a collection of symptoms that result from increased permeability of the glomerular capillary walls.[1-4] In contrast, the nephritic syndrome is a collection of symptoms that result from glomerular inflammation.[1-3,5] Both syndromes are caused by immune-mediated injury to the kidney glomerulus.[1,2,5,6]

Although cell-mediated immunity plays a role in certain glomerulopathies, most are the result of antibody-mediated mechanisms.[1,5,6] In antibody-mediated glomerular injury, antibodies either react locally, forming immune complexes in situ, or are circulating and form complexes in the bloodstream that later become trapped within the glomeruli.[1] Regardless of the site of their formation, these antigen–antibody complexes deposit in various parts of the glomeruli. To best appreciate this, an understanding of glomerular anatomy is essential and is reviewed here.

The glomerulus is an anastomosing arrangement of capillaries lined directly by a fenestrated endothelium then 2 layers of epithelium—visceral and parietal—that encapsulate Bowman's space, where glomerular filtrate collects.[1,3,5] The entire glomerular tuft is supported by mesangium, a group of cells that lie between the capillaries.[1,3,5] Immune complexes may deposit between the visceral epithelial cells and the glomerular capillary wall (subepithelial space), between the glomerular capillary wall and the endothelium (subendothelial space), or in the mesangium.

The site of immune complex deposition gives rise to the varied histology of glomerular disease. For instance, immune complex deposits confined to the subepithelial space, as seen in some cases of nephrotic syndrome, are not exposed to blood elements, and generally do not have an inflammatory pathology.[1,6] Deposits in the subendothelial space and mesangium, however, are accessible to the circulation and elicit the inflammatory response seen in most causes of nephritic syndrome.[1,6]

How Does the Pathophysiology of Nephrotic Syndrome Explain Its Clinical Presentation? How Does the Pathophysiology of Nephritic Syndrome Explain Its Clinical Presentation?

In nephrotic syndrome, capillary wall derangement allows protein—notably albumin—to leak from the bloodstream into the urine, causing immense proteinuria (in excess of 3.5 g/d) and consequent hypoalbuminemia.[1,3] This depletion of protein in the bloodstream decreases capillary oncotic pressure, which promotes fluid movement from the bloodstream into the interstitium (causing generalized edema) or into body cavities such as the thorax or abdomen (causing pleural effusion or ascites).[1,3] As fluid leaves the bloodstream, a decrease in the effective circulating volume is seen.[1,3] This decrease in vascular volume leads to a decrease in renal plasma flow and subsequently a decrease in glomerular filtration.[1,3] A decreased glomerular filtration rate stimulates the renin–angiotensin–aldosterone system and ultimately leads to an increase in sodium and water retention, which further aggravates the edema.[1,3]

Additionally, the hypoalbuminemia stimulates increased synthesis of lipoproteins by the liver, resulting in hyperlipidemia.[1,3] The mechanism behind this synthesis is not yet fully understood, but is not a simple compensatory mechanism,

given that lipoproteins will not sufficiently increase the plasma oncotic pressure to normal because of their large size.[7]

In nephritic syndrome, inflammatory processes damage the entire glomeruli, which allows spillage of red blood cells (hematuria) and protein into the urine.[1,3] Of note, the proteinuria seen in nephritic syndrome is notably less than that seen in nephrotic syndrome because the inflamed glomeruli somewhat limit the passage of protein.[1,3] As the damaged glomeruli are unable to appropriately filter the plasma flow, there is an increase in the blood urea nitrogen and creatinine concentrations (azotemia). Moreover, there is a decrease in the production of urine (oliguria) and consequent rise in capillary hydrostatic pressure.[1,3] Elevated hydrostatic pressure leads to hypertension and stimulates fluid movement from the bloodstream to the interstitium, which leads to edema.[1,3] The edema may also be a result of the proteinuria (via the same mechanism discussed with nephrotic syndrome).

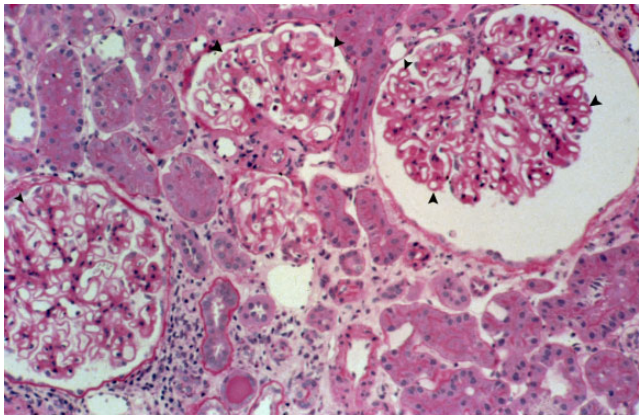

Figure 1. Normocellular glomeruli demonstrating thickening of the capillary walls (arrrowheads). (H&E stain, intermediate magnification).

Diagnostic Findings, Part 3

What Is the Next Step in Determining the Cause of the Patient's Nephrotic Syndrome?

A renal biopsy is indicated. The sample contained one core of renal cortex that contained 9 glomeruli. Light microscopy showed diffuse thickening of the glomerular capillary walls throughout all of the glomeruli. The endothelium, mesangium, and interstitium were unremarkable. No proliferative features were seen (Figures 1-3). Basement membrane spikes were evident with methenamine silver stain (Figure 3). Immunofluorescence microscopy demonstrated a diffuse granular pattern that stained positive for IgG and C3 (Figure 4). Electron microscopy demonstrated subepithelial basement membrane electron-dense deposits (antigen–antibody complexes) (Figure 5). Based on the findings on light, electron, and immunofluorescence microscopy, the diagnosis of membranous nephropathy was made.

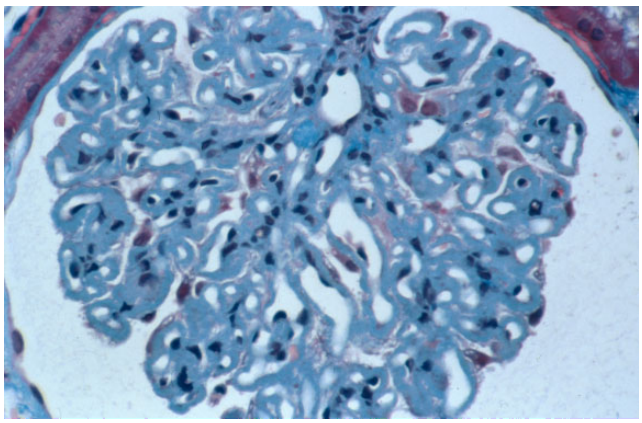

Figure 2. Diffuse thickening of the glomerular capillary wall is seen with no hypercellularity. (Trichrome stain, high power magnification).

Questions/Discussion Points, Part 3

What Is Membranous Nephropathy? How Does the Disease-Specific Pathogenesis Explain Its Morphological Presentation and What Is the Disease Treatment?

Membranous nephropathy, one of the primary diseases that cause nephrotic syndrome, occurs when immune complexes deposit within the subepithelial space and subsequently damage the glomerular visceral epithelial cells.[1,3,6,8] These highly specialized cells—commonly called podocytes—shroud the glomerular capillaries and possess long processes (called foot processes) that interdigitate and form filtration slits.[1,3,6,8] The filtration slits maintain the glomerular filtration barrier by filtering proteins based on size.[1,3] As such, injury to these cells results in the massive proteinuria seen in nephrotic syndrome.[1,3]

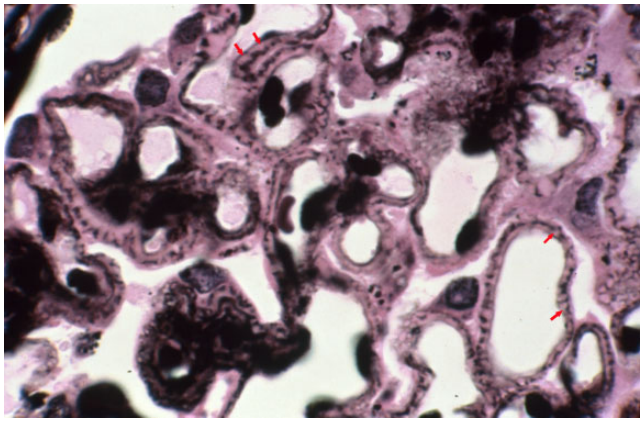

Figure 3. Normocellular glomerulus with diffuse thickening of the capillary wall. The basement membrane matrix that stains positive with the silver stain is seen extending between the subepithelial deposits (red arrows; silver methenamine stain, high power magnification).

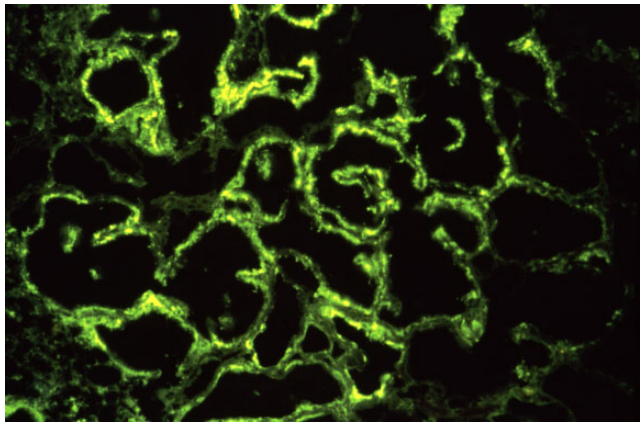

Figure 4. Immunofluorescence microscopy demonstrating a diffuse granular pattern for IgG along the glomerular capillary wall.

Table 1. Incidence of Primary Diseases That Cause Nephrotic Syndrome in Adults.[1,3-5]

Primary Diseases	Approximate Incidence in Adults (% of Primary Disease)	Approximate Incidence in Adults (% of All Diseases That Cause Nephrotic Syndrome)
Minimal change disease	10	6
Focal segmental glomerulonephritis	35	21
Membranous nephropathy	30	18
Membranoproliferative glomerulonephritis	5	3
Other	20	12
Approximate prevalence of primary disease in adults (%)		60

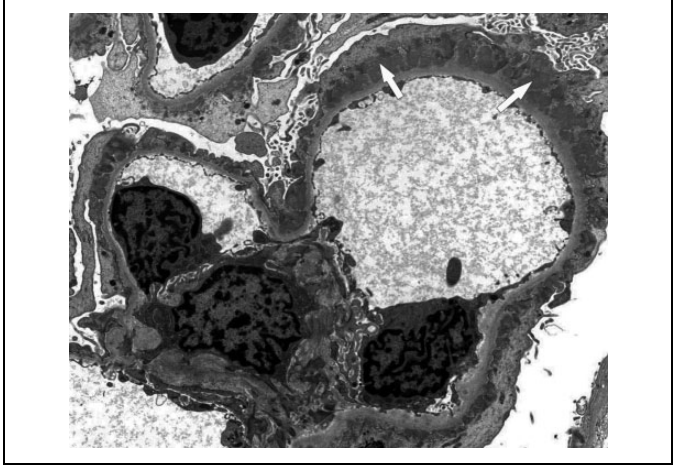

Figure 5. Electron micrograph demonstrating subepithelial electron-dense deposits in the basement membrane (white arrows) along with fusion of the epithelial cell foot processes.

The immune complexes that form in membranous nephropathy may be in response to exogenous or endogenous antigens or to a renal autoantigen, the phospholipase A_2 receptor.[1,3,5-7] As these complexes deposit in the subepithelial space, thickening of the basement membrane is seen on light microscopy.[1,3,6] Over time, additional basement membrane is laid down between the deposits, giving the appearance of protruding spikes.[1,3,6] Eventually, the additional membrane material closes over the deposits, further thickening the basement membrane and effacing part of the overlying podocytes, which can be visualized on electron microscopy.[1,3,6] As the immune complexes deposit randomly within the subepithelial space, a diffuse granular pattern is seen on immunofluorescence.[1,3,6]

The disease prognosis is determined by the level of risk (low, moderate, or high) of progressive decline in renal function and is treated with either conservative nonimmunosuppressive therapy or immunosuppressive therapy.[7,8] While nonimmunosuppressive therapy is administered to nearly all patients with membranous nephropathy, immunosuppressive therapy is given only to those who remain at a moderate or high risk of progression of renal function decline.[7,8]

What Are the Other Diseases That Cause Nephrotic Syndrome and What Is Their Prevalence? What Are the Diseases That Cause Nephritic Syndrome?

The occurrence of nephrotic syndrome in adults is 3 per 100 000 persons (0.003%) per year.[4] In addition to membranous nephropathy, the other primary diseases that cause nephrotic syndrome are minimal change disease, focal segmental glomerulosclerosis, and membranoproliferative glomerulonephritis.[1,3,5] In adults, primary disease accounts for approximately 60% of cases.[1] Refer to Table 1 for the disease incidence of each. Secondary causes of nephrotic syndrome in adults, which account for 40% of cases, commonly include diabetes mellitus, systemic lupus erythematosus, and amyloidosis, with other less common causes being infection and malignancy.[1,3,5]

The diseases that commonly cause nephritic syndrome include postreptococcal (or other postinfectious) glomerulonephritis, IgA nephropathy, antiglomerular basement membrane disease, and the small vessel vasculitides (eg, granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis).[1,3,5]

How Are the Nephrotic and Nephritic Syndromes Diagnosed?

Generally, a diagnosis of nephrotic syndrome is made after urine tests—urinalysis and 24-hour urine collection—have shown nephrotic-range proteinuria and blood chemistries have shown hypoalbuminemia and possibly hyperlipidemia.[2,4,8] Follow-on laboratory tests and/or a renal biopsy—examined

with light, electron, and immunofluorescence microscopy—are often performed to determine etiology and guide management.[2,4,8]

A diagnosis of nephritic syndrome is achieved via a similar method. Urinalysis will show hematuria and proteinuria, while blood chemistries will show azotemia, quantified through blood urea nitrogen and creatinine levels.[2] Follow-on laboratory tests and imaging studies may be performed to determine whether the nephritis is from a primary or secondary cause.[2] Finally, a renal biopsy may be done if etiology is still uncertain.[2]

What Are the Morphological Aspects of Renal Biopsies of Patients With Nephrotic Syndrome? How Do They Differ From Renal Biopsies of Patients With Nephritic Syndrome?

As previously mentioned, the morphological presentation of glomerular disease is diverse. The general characteristics of renal biopsies in patients with a glomerulopathy are discussed here, while specific presentations are found in Table 2.

On light microscopy, glomerular injury is described by its location in the glomerulus and by its prevalence in the biopsy sample.[1,3,6] Injury involving only a portion of the glomerulus is said to be segmental, while that which involves the entire glomerulus is global.[1,3,6] Injury involving only some of the glomeruli in the sample is said to be focal, while that which involves most or nearly all of the sample's glomeruli is diffuse.[1,3,6]

Additionally, glomerular injury may cause hypercellularity either from an increase in the number of endothelial or mesangial cells (proliferative) or from an influx of leukocytes from the circulation (exudative).[1,3,6] Basement membrane thickening, caused by immune complex deposition then formation and addition of new basement membrane material, may also be seen.[1,3,6] This thickening is typically observed in more chronic forms of glomerular injury.[1,3,6]

Hyalinosis and sclerosis are 2 other tissue responses seen in long-standing injury to the glomerulus.[1,3,6] Hyalinosis is the accumulation of hyalin, a homogenous composition of plasma proteins, while sclerosis is the hardening of tissue from abnormal extracellular matrix deposition.[1,3,6] Both responses can cause obstruction and obliteration of glomerular capillary lumens.[1,3,6]

As light microscopy is used for a general assessment of glomerular injury, electron and immunofluorescence microscopy provide a more focused evaluation. Electron microscopy is largely used for visualization of the basement membrane and localization of immune deposits, which present as homogenous and electron-dense.[1,3,6] Immunofluorescence microscopy is used to further examine these deposits by detecting the presence of certain immune reactants including antibodies such as IgG, IgA, and IgM and complement proteins such as C3, C4, and C1q.[1,3,6]

What Are Complications of Nephrotic Syndrome? What Are the Complications of Nephritic Syndrome?

There are several complications of nephrotic syndrome, including thrombotic and thromboembolic events, infection, cardiovascular disease, hypovolemic crisis, and acute renal failure.[1,2,4] The most common of these, thrombosis and thromboembolism,[9] are discussed below.

Several coagulation proteins have altered levels in nephrotic syndrome.[1,2,4,9] As certain endogenous anticoagulants such as antithrombin III and proteins C and S are lost in the urine at increased levels, the liver upregulates synthesis of certain coagulation proteins such as factors V and VII, fibrinogen, and von Willebrand factor.[1,2,4,9] Together, these aberrations lead to a hypercoagulable state, increasing the risk of deep vein thrombosis, renal vein thrombosis, and pulmonary embolism.[1,2,4,9] Notably, renal vein thrombosis is most common in membranous nephropathy, affecting approximately 30% of patients.[9]

In nephritic syndrome, the most notable complications occur as the symptoms of hypertension and renal insufficiency worsen if not properly managed.[1,2]

Teaching Points

- Immune-mediated mechanisms, particularly those involving immune complexes, underlie most glomerular diseases.
- Immune complexes that deposit in the glomerulus generally localize within the subepithelial space, subendothelial space, or mesangium.
- The site of immune complex deposition within the glomerulus determines the morphology and clinical presentation of the disease.
- Nephrotic syndrome is a collection of symptoms that results from increased permeability of the glomerular capillary walls.
- The tetrad of proteinuria, hypoalbuminemia, generalized edema, and hyperlipidemia characterize the nephrotic syndrome.
- Nephritic syndrome is a collection of symptoms that results from inflammatory damage of the glomeruli.
- Hematuria, azotemia, oliguria, hypertension, proteinuria, and edema characterize the nephritic syndrome.
- Diffuse thickening of the glomerular capillary wall caused by subepithelial immune complex deposits are the morphological findings of membranous nephropathy.
- The diseases that cause nephrotic syndrome are classified as either primary or secondary. The primary causes commonly include minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, and membranoproliferative glomerulonephritis. Common secondary causes include diabetic nephropathy, systemic lupus erythematosus, and amyloidosis.

Table 2. Morphologic Findings of Common Glomerulopathies.[1-3,5,6]

		Light Microscopy	Electron Microscopy	Immunofluorescence Microscopy
Primary glomerular diseases	Common causes of nephrotic syndrome			
	Minimal change disease	Normal	No deposits, podocyte effacement	No immune deposits
	Focal segmental glomerulonephritis	Focal, segmental lesions	No deposits, podocyte effacement	No immune deposits
	Membranous nephropathy	Diffuse capillary wall thickening with no hypercellularity	Diffuse subepithelial deposits	Diffuse granular capillary wall IgG and C3
	Membranoproliferative glomerulonephritis	Diffuse capillary wall thickening with hypercellularity	Diffuse subendothelial deposits	Diffuse granular capillary wall complement, possible IgG
	Common causes of nephritic syndrome			
	IgA nephropathy	Diffuse mesangial lesions with mesangial hypercellularity	Diffuse mesangial deposits	Diffuse granular mesangial IgA
	Antiglomerular basement membrane disease	Focal necrosis and crescents	No deposits	Diffuse linear capillary wall IgG
Secondary glomerular diseases	Postinfectious glomerulonephritis	Diffuse enlarged glomeruli, proliferative and exudative endothelial and mesangial hypercellularity	Diffuse subepithelial hump-like deposits	Diffuse granular IgG and C3 in capillary wall and mesangium
	Small-vessel vasculitides	Focal necrosis and crescents	No deposits	No immune deposits

- The diseases that cause nephritic syndrome include poststreptococcal glomerulonephritis and other postinfectious causes, IgA nephropathy, antiglomerular basement membrane disease, and the small vessel vasculitides.
- A diagnosis of nephrotic or nephritic syndrome is achieved through a combination of patient history, physical examination, and serum and urine studies. A renal biopsy is often done to determine etiology.
- A full assessment of a renal biopsy includes evaluation by light, electron, and immunofluorescence microscopy.
- Important complications of nephrotic syndrome are thrombotic and thromboembolic events, while hypertension and renal insufficiency are the primary complications seen with nephritic syndrome.

Acknowledgment

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Declaration of Conflicting Interests

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Educational Case: Immune-Related Disorders of the Bowel: Celiac Disease

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, gastrointestinal tract, immune-related disorders of the bowel, celiac disease, collagenous sprue, villous blunting, serologic studies

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Primary Objective

Objective GT5.2: Celiac Disease. Explain the pathophysiology of gliadin hypersensitivity (celiac disease).

Competency 2: Organ System Pathology; Topic GT: Gastrointestinal Tract; Learning Goal 5: Immune-Related Disorders of the Bowel.

Patient Presentation

A 30-year-old otherwise healthy woman presents with malodorous diarrhea of 6 months' duration. It is sometimes associated with abdominal cramps and bloating. It has been getting worse in the past month, and she also reports a 10-pound weight loss and chronic fatigue. She is a frequent traveler and experienced diarrhea during a trip to Canada last summer, which resolved within a few days. She denies nausea, vomiting, constipation, dark stool, or blood in stool. The patient is lactose intolerant, but denies consuming lactose containing dairy products in past 6 months. She has not changed her diet in any other way. She is not taking nonsteroidal anti-inflammatory drugs (NSAIDs) or any other over-the-counter medications. No one else in her family has similar symptoms. She has a cousin with Crohn disease. Physical examination reveals no fever. The abdomen is soft, nontender and nondistended, without masses or organomegaly. The bowel sounds are normal.

Diagnostic Findings, Part 1

The patient's primary care physician ordered some screening tests. Complete blood count revealed hemoglobin 11.8 g/dL (reference range 14.0-17.4 g/dL) and mean corpuscular volume 76 fL (reference range 80.0-96.0 fL). Iron level was 30 µg/dL (reference range 65-175 µg/dL). The stool occult blood, culture, and ova and parasite tests were negative. Liver function tests and fecal calprotectin (a marker for intestinal inflammation and surrogate marker of inflammatory bowel disease) were within normal ranges. Serum immunoglobulin A (IgA), IgG, and IgM levels were within normal ranges.

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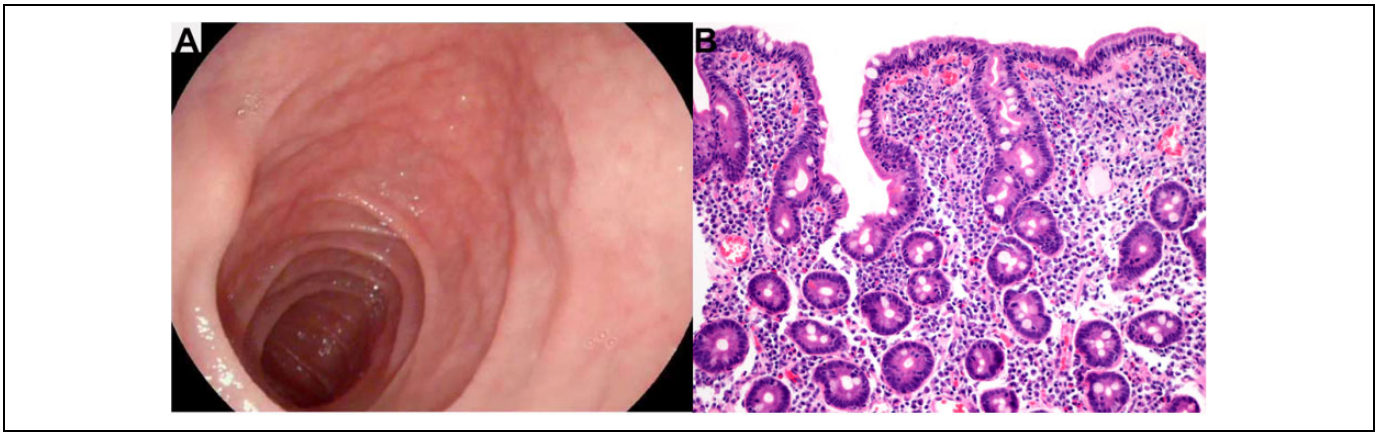

Figure 1. A, Endoscopic view of duodenal mucosa. B, Duodenal biopsy (hematoxylin and eosin stain; original magnification: 20×).

Questions/Discussion Points, Part 1

What Diseases Would You Consider in Your Differential Diagnosis?

Since the patient is a frequent traveler, and she has a medical history of lactose intolerance and family history of Crohn disease, chronic parasitic infection, food sensitivities, and inflammatory bowel disease are important considerations. Other common differential diagnoses for chronic diarrhea include celiac disease, chronic viral or bacterial infections, irritable bowel syndrome, microscopic colitis, autoimmune enteropathy, and primary immunodeficiency. However, the foregoing initial screening results make infection, inflammatory bowel disease, and immunodeficiencies unlikely explanations for her symptoms.

Diagnostic Findings, Part 2

Further autoimmune workup revealed anti-tissue transglutaminase (anti-TTG) IgA >128 U/mL (reference range <10 U/mL), anti-deamidated gliadin peptide (anti-DGP) IgA > 142 U/mL (reference range <10 U/mL), and anti-DGP IgG >302 U/mL (reference range <10 U/mL).

Questions/Discussion Points, Part 2

How do the Additional Laboratory Findings Help You Narrow the Differential Diagnosis?

The above serology results make celiac disease highly likely. Screening for IgA anti-TTG antibodies is the first-line test for celiac disease. This may be performed in conjunction with serum IgA levels since patients with selective IgA deficiency may have false negative TTG results. The presence of IgA-endomysial antibodies (EMA) supports the diagnosis in patients with equivocal TTG titers.[1] Assays for IgG-TTG, IgG-DGP, and IgG-EMA are available for IgA deficient patients, a group at increased risk for development of celiac disease.

Serologic studies display suboptimal specificity for celiac disease. Elevated anti-TTG and anti-EMA alone are insufficient to diagnose this disorder, and biopsy confirmation is required.[2] Furthermore, a small percentage of patients with negative serologies prove to have celiac disease.[3] This may occur in patients with primary immunodeficiencies (eg, common variable immunodeficiency, selective IgA deficiency), those on therapeutic immunosuppression, or early in the disease course. Seronegativity was recently described in patients with severe, long-standing disease in whom anti-TTG antibodies were bound to the small intestinal mucosa and sequestered from circulation.[4] At present, serology is considered a diagnostic modality, whereas endoscopic duodenal biopsy represents the gold standard.

What Is Recommended Next for Evaluation of This Patient?

The patient was referred to a gastroenterologist for upper gastrointestinal endoscopy evaluation. The gastric mucosa appeared normal endoscopically. The duodenal endoscopy and biopsy findings are shown in Figure 1.

Diagnostic Findings, Part 3

What Are the Abnormalities Present in Figure 1? What Are the Possible Explanations of the Histologic Findings in Figure 1B?

Figure 1A shows mildly scalloped mucosa in the second portion of the duodenum. This alteration is common in patients with celiac disease. Figure 1B shows a duodenal biopsy sample (hematoxylin and eosin stain) displaying partially effaced villous architecture, increased intraepithelial lymphocytes and hyperplastic crypts. While these histologic findings suggest celiac disease, by themselves they are insufficient to distinguish celiac disease from its mimics, as discussed subsequently. However, based on the positive serologic studies and characteristic histologic features, a diagnosis of celiac disease

was rendered in the case at hand. The patient was put on gluten-free diet. After 8 weeks, the symptoms improved substantially.

Questions/Discussion Points, Part 3

What Is the Pathophysiology of Celiac Disease?

Celiac disease is an allergic response to dietary gluten in genetically susceptible individuals. Gluten is partially digested into a mix of complex proteins, including gliadins and glutenins, by intestinal enzymes. Gliadins cause increased intestinal permeability by binding to the CXCR3 chemokine receptor on enterocytes and causing release of zonulin, which transiently weakens intercellular junctions. Undigested peptides leak into the lamina propria where they are further broken down by tissue transglutaminase. Resultant deaminated gluten fragments may be recognized as pathogens, in some individuals, and presented to CD4+ T cells by human leukocyte antigen (HLA) DQ2/8-bearing antigen presenting cells.[5] This activates Th2 cells and leads to B cell proliferation and Th1-mediated cytokine release. Inflammation-mediated damage to the intestinal epithelium allows passage of more gluten fragments into the mucosa and incites a self-sustaining inflammatory response.[6] Elimination of dietary gluten is the only effective treatment.

What Genetic Features Are Associated With Celiac Disease?

Patients with celiac disease often harbor HLA DQ2 and DQ8 alleles. In fact, HLA genotyping may be used as a screening test for children at risk for celiac disease.[7] Absence of these alleles essentially excludes the diagnosis, particularly in asymptomatic patients. The risk of celiac disease is 1 in 10 for first-degree relatives of affected patients, a substantial increase over the 1% prevalence observed in the United States population.[8,9]

Which Other Disorders Are Associated With Celiac Disease?

Patients with Down syndrome, Turner syndrome, and those with other immune-mediated disorders, such as autoimmune thyroid disease and type 1 diabetes are at increased risk for celiac disease. Patients with celiac disease frequently have extraintestinal manifestations. Iron deficiency anemia results from inadequate iron absorption in the duodenum.[10] Dermatitis herpetiformis is a blistering skin disease which is associated with celiac disease.[11] Peripheral neuropathy and ataxia may result from impaired small intestinal uptake of vitamin B12 and folate. Osteoporosis and infertility are also associated with gluten sensitivity.[1]

What Would You Expect to See in Endoscopic Biopsy Samples From the Duodenum?

The normal duodenal mucosa displays circumferential folds called "plicae circularis" that are oriented perpendicular to the long axis of the small intestine; these facilitate absorption of ingested nutrients (Figure 2A). Histologically, the mucosa is organized into villous projections with a core of lamina propria lined by absorptive cells and goblet cells and downward extensions of epithelium between villi, called crypts (Figure 2B). The crypts are lined by similar epithelia, as well as Paneth and endocrine cells (Figure 2C). The normal villous to crypt ratio is approximately 3-4:1. Intraepithelial CD8+ T cells normally number approximately 20 per 100 enterocytes, or 1 T lymphocyte per 6 enterocytes.[12] They display a "decrescendo pattern" of distribution, meaning that their density is lower at the villous tips compared to crypt bases (Figure 2D). The lamina propria also contains abundant plasma cells and lymphocytes and occasional neutrophils and eosinophils.

Small intestinal samples from patients with celiac disease display varying degrees of intraepithelial lymphocytosis, villous shortening/blunting, increased lymphoplasmacytic lamina propria inflammation, and crypt hyperplasia. Early or milder cases of celiac disease may display normal villous architecture and only increased intraepithelial lymphocytes (Figure 3A and B). Better-developed cases show markedly shortened or completely effaced villi (Figure 3C), elongated and hyperplastic crypts (Figure 3D), and lamina propria expansion by chronic inflammation (Figure 3D). Although occasional intraepithelial neutrophils may be present, this is not a prominent feature of celiac disease.

What Disorders Are in the Histologic Differential Diagnosis of Celiac Disease?

Other disorders such as peptic duodenitis, tropical sprue, common variable immunodeficiency, autoimmune enteropathy, and small intestinal Crohn's disease share histologic features with celiac disease, namely villous blunting and intraepithelial lymphocytosis. Peptic duodenitis typically occurs in the setting of gastric *Helicobacter pylori* infection or reactive gastropathy due to NSAIDs or other gastric irritants. Intraepithelial lymphocytes are only minimally increased and foveolar metaplasia of the surface epithelium is almost uniformly seen. Tropical sprue is a rare disorder that is thought to be due to an unidentified microbe. It displays all of the features of celiac disease, although they may be more pronounced in the ileum compared to the duodenum.[13] Patients with common variable immunodeficiency have markedly decreased levels of circulating immunoglobulins, and biopsy samples throughout the gastrointestinal tract may display a decrease or absence of plasma cells.[14] Autoimmune enteropathy is more common in young males who may have circulating autoantibodies to goblet cells or parietal cells. Biopsy samples may also display loss of goblet cells or parietal cells.[15] Finally, Crohn disease is characterized by abnormal chronic (lymphocytes, plasma cells) and active (neutrophil-rich) intestinal inflammation, and architectural remodeling. Non-necrotic epithelioid granulomas are the most helpful diagnostic findings, but this feature is inconsistently present.

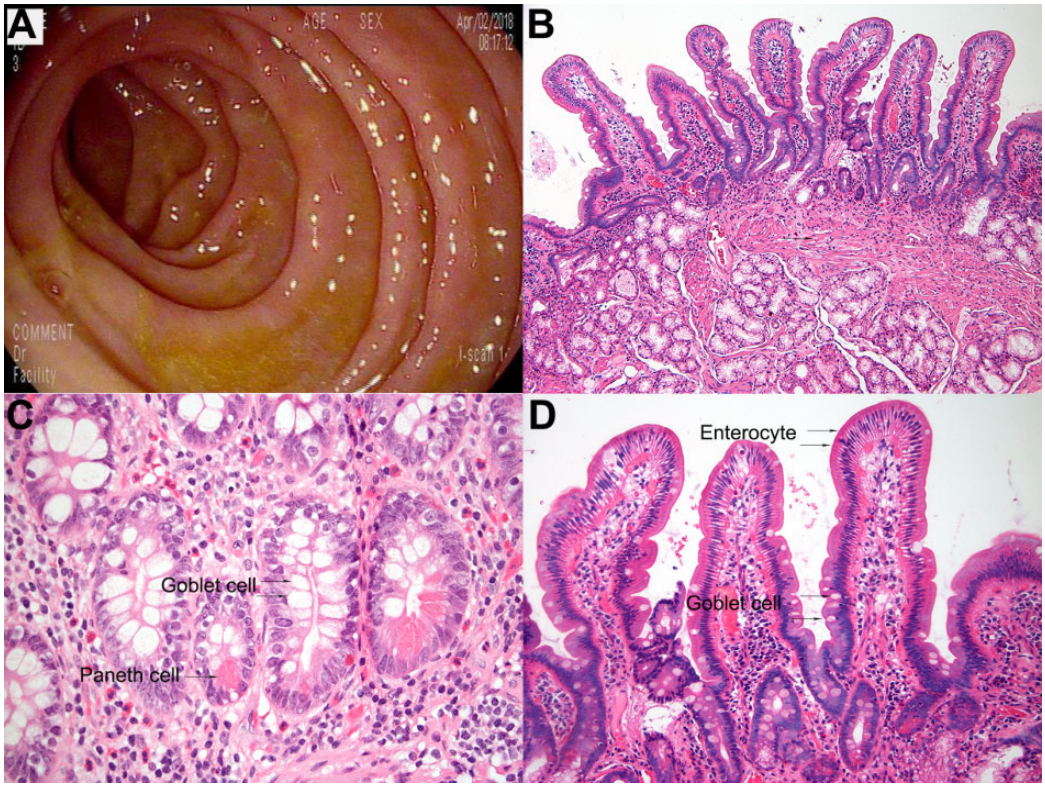

Figure 2. Normal duodenal mucosa. A, Endoscopic view of normal duodenum with smooth mucosa and circumferential intestinal folds (plicae circularis). B, Normal duodenal mucosa with slender villi and villus to crypt ratio of 3-4:1, and underlying submucosal Brunner's glands (hematoxylin and eosin stain; original magnification: 10×). C, High power view of duodenal crypts showing goblet cells and Paneth cells (hematoxylin and eosin stain; original magnification: 40×). D, Normal duodenal villi with scattered intraepithelial lymphocytes more prominent in the base (hematoxylin and eosin stain; original magnification: 20×).

What Is the Natural History of Celiac Disease?

The vast majority of patients experience resolution of signs and symptoms of celiac disease shortly after gluten withdrawal. Only 1% to 2% experience refractory celiac disease defined as persistent or recurrent symptoms despite adherence to gluten-free diet for 6 to 12 months. Refractory celiac disease comprises 2 subgroups; intraepithelial T cells display normal coexpression of CD3 and CD8 in type 1 refractory celiac disease, whereas CD8 expression is lost in type 2 disease.[16] The latter group is at risk for progression to enteropathy-associated T-cell lymphoma, an aggressive malignancy with <20% five-year overall survival.[17] The risk of intestinal lymphoma is 6 to 7-fold higher in patients with celiac disease compared to the general population.[18] So-called "collagenous sprue" is a pattern of injury that may be seen in refractory celiac disease (Figure 4), but can also be seen in patients with hypersensitivity to other dietary proteins or, rarely, as a hypersensitivity reaction to angiotensin II receptor antagonists.[19] Thus, this pattern is not necessarily indicative of gluten sensitivity and patients with the finding of collagenous sprue may or may not benefit from gluten withdrawal. Patients with long-standing, untreated celiac disease are at more than 4-fold increased risk for small intestinal adenocarcinoma.[20] Although the mechanism of carcinoma development is incompletely understood, recent studies suggest a role for mismatch repair deficiency in these cases.[21]

What Is the Role of Gluten-Free Diet on the Treatment of Celiac Disease?

At present, gluten-free diet is the only effective treatment for celiac disease. Gluten-free diet is a diet that strictly excludes gluten, a composite of storage proteins termed prolamins and glutelins found in wheat, barley, rye, oat, and other related grains. Strict adherence to the gluten-free diet can help to meet the therapeutic goals in almost all patients with celiac disease. However, adhering to a gluten-free diet is challenging, especially for young adults. Many factors including cultural background, social isolation, financial burden of purchasing gluten-free foods, and incorrect/lack of food labeling have contributed to the nonadherence. Regular dietetic follow-up and utilization of gluten-free food database can be helpful to improve adherence.[22,23]

Adoption of gluten-free diets and consumption of gluten-free foods have risen substantially in the United States over the past 3 decades.[24] This is due, in part, to increased awareness of celiac disease. Elimination of gluten and wheat from the diet

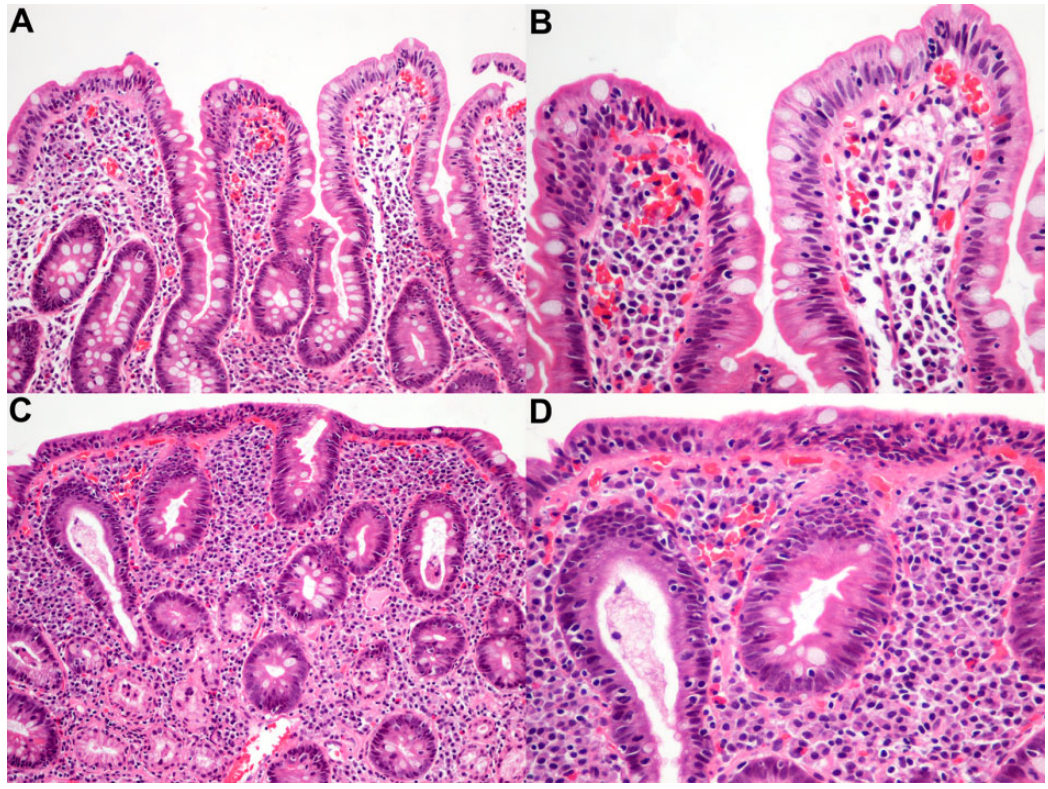

Figure 3. Celiac disease. A and B, Celiac disease with mild villous blunting and increased intraepithelial lymphocytes particularly in the villous tips (hematoxylin and eosin stain; original magnification: A, 20×; B, 40×). C and D, Celiac disease with almost completely blunted villi, marked intraepithelial lymphocytosis, hyperplastic crypts, and expanded lamina propria by chronic inflammation (hematoxylin and eosin stain; original magnification: C, 20×; D, 40×).

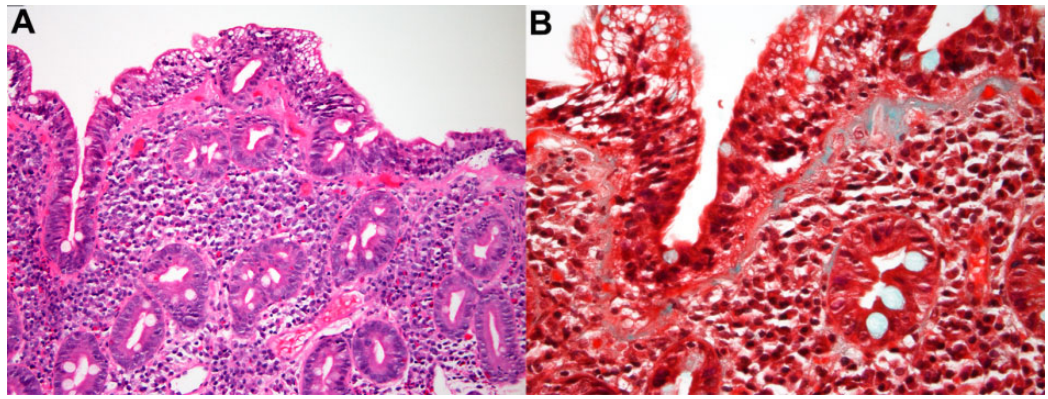

Figure 4. Collagenous sprue. A, Duodenal mucosa with typical features of celiac disease and irregularly thickened subepithelial collagen (hematoxylin and eosin stain; original magnification: 40×). B, A trichrome stain highlighting the thick and irregular subepithelial collagen with entrapped capillaries (original magnification 40×).

alleviates gastrointestinal symptoms in some individuals who do not have celiac disease. These groups are now said to have nonceliac gluten sensitivity and nonceliac wheat sensitivity, respectively.[25,26] Emerging evidence suggests that avoidance of gluten may benefit patients with certain psychiatric disorders, atopic diseases, endometriosis, and fibromyalgia.[24]

The gluten-free lifestyle is also gaining popularity among healthy individuals. Although gluten avoidance may contribute to weight loss, other health benefits have not been convincingly shown. Indeed, some evidence suggests that gluten-free diets exacerbate cardiovascular disease by reducing intake of beneficial whole grains.[27]

Teaching Points

1. Celiac disease is a multifactorial disorder that demonstrates the interplay between genetic and environmental factors in immune-mediated diseases.
2. The diagnosis of celiac disease relies upon serologic evaluation of increased antibodies against TTG, EMA, and DGP; duodenal biopsy confirmation of villous shortening/blunting; intraepithelial lymphocytosis; crypt hyperplasia; and clinical evaluation of patient's response to gluten-free diet. This underscores the importance of interdisciplinary communication in the management of gastrointestinal disorders.
3. Like many gastrointestinal disorders, celiac disease has extraintestinal manifestations related to immune dysregulation, such as dermatitis herpetiformis, and nutritional deficiencies such as iron-deficiency anemia.
4. Celiac disease displays a spectrum of histologic abnormalities ranging from normal mucosal histology and villous architecture, to mild intraepithelial lymphocytic infiltration and partial villous atrophy, to marked lymphocytosis and total villous blunting, related to disease duration and severity. 5. Recognition of celiac disease is clinically important since gluten withdrawal is the only effective therapy, and untreated disease can lead to potentially serious sequelae including severe malnutrition, lymphoma, and adenocarcinoma.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Educational Case: Symptomatic but Unruptured Abdominal Aortic Aneurysm

Aldis H. Petriceks, BA[1], John C. Olivas, BS[1], and Darren Salmi, MD[1,2]

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, abdominal aortic aneurysm, aortic dissection, aneurysm risk factors, unruptured aneurysm, ruptured aneurysm, complications of abdominal aortic aneurysms, classification of aortic dissections

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Primary Objective

Objective CBV2.3: Abdominal Aortic Aneurysm: Describe the clinical consequences of an abdominal aortic aneurysm.

Competency 2: Organ System Pathology; Topic: Cardiovascular—Blood Vessels (CBV); Learning Goal 2: Vascular Damage and Thrombosis.

Secondary Objective

Objective CBV2.2: Aortic Aneurysm and Dissection: Compare and contrast aortic aneurysms and aortic dissections in terms of their predisposing factors, the sites of involvement, and patient populations likely to be affected.

Competency 2: Organ System Pathology; Topic: Cardiovascular—Blood Vessels (CBV); Learning Goal 2: Vascular Damage and Thrombosis.

Patient Presentation

A 68-year-old male patient presents to the emergency department with nausea and a pulsating pain in his right groin. He reports intermittent bouts of syncope in the past week, which he never had previously. He also has chronic lower back pain but states that the pain is now more severe and radiates from belly to back and is very different from his usual back pain. Further interview reveals that the patient has smoked approximately 10 cigarettes per day for the past 30 years. He is in visible distress, although alert and oriented. His vital signs are remarkable for hypertension, with a blood pressure of 170/115.

Diagnostic Findings, Part I

Physical examination of the right groin reveals a small pulsatile mass. Abdominal palpation is suboptimal because of the patient's size. Auscultation of the abdomen reveals an intermittent bruit, audible during systole, and dependent on heart rate.

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Question/Discussion Points, Part I

Discuss the Differential Based on the Clinical Presentation

The patient presents with nausea, hypertension, syncope, increasing lower back pain, and pulsing unilateral groin pain. With his obesity, age, and history of hypertension, the patient likely suffers from atherosclerosis as well. His alertness and orientation suggest he is hemodynamically stable. These factors and symptoms suggest a possible abdominal aortic aneurysm (AAA). The particularly important risk factors in this patient's history are as follows: (1) his advanced age, as AAA is rare in persons younger than 60 years[1]; (2) his hypertension, as high blood pressure can induce small tears in the extracellular matrix (ECM), leading to smooth muscle cell (SMC) recruitment, vascular thickening, reduced vascular compliance, and ultimately aneurysm[2]; (3) his smoking history, as smoking is the dominant behavioral risk factor for AAA[3]; and (4) the likelihood that he also suffers from atherosclerosis, which is the dominant physiological risk factor for AAA. This is because atherosclerotic plaques weaken the arterial wall through a combination of chronic inflammatory response and ischemia of the underlying media.[2]

The most important signs and symptoms from his clinical presentation are (1) the patient's novel and increasing lower back pain, (2) his pulsing unilateral groin pain and palpable mass, and (3) his absence of hypovolemic shock symptoms (eg, hypotension, decreased alertness), suggesting that any presumptive aneurysm has not ruptured.[2,4]

However, the differential diagnosis still includes the following: aortic dissection (AD), pancreatitis (particularly because of the radiating lower back pain), ischemic bowel, renal colic, gastrointestinal hemorrhage, pyelonephritis, and peptic ulcer disease.

The physical examination does little to narrow this differential, as obesity makes a thorough abdominal examination difficult. Nonetheless, given the history and clinical presentation—smoking, hypertension, age, obesity, back and groin pain, nausea—AAA is the most prominent concern. The unilateral groin pain could result from an associated aneurysm of the right common iliac artery—a regular finding in AAA—adding isolated iliac aneurysm to the differential.[4] Therefore, the most likely diagnosis is an unruptured AAA with associated unruptured isolated right common iliac aneurysm. The patient is clearly symptomatic and should be evaluated for possible or imminent rupture. One should note that the diagnosis, to this point, has been based on clinical findings.

What Further Testing Is Indicated for This Patient?

In hemodynamically unstable patients, timely diagnoses might preferably be reached via ultrasound. However, computed tomography (CT) imaging is the preferred method for this hemodynamically stable patient because (1) CT provides a more detailed and accurate assessment of the internal abdominal structures, while also showing relevant vessels and organs that may be involved with the aneurysm. This is one reason why the Society for Vascular Surgery (SVS) recommends CT for the assessment of maximum AAA diameter.[5] (2) Computed tomography imaging offers less variability in technician skill and methodology. (3) There are certain regions of the body where ultrasound is affected by overlying tissue—for instance, the iliac arteries, where overlying bowel can interfere with the imaging process.[6]

Therefore, CT scans should be performed to evaluate dilation of the patient's aorta and/or other major arteries. The thorax, abdomen, and lower limbs should all be evaluated to ensure full coverage of possible aneurysms, dissections, or embolisms.

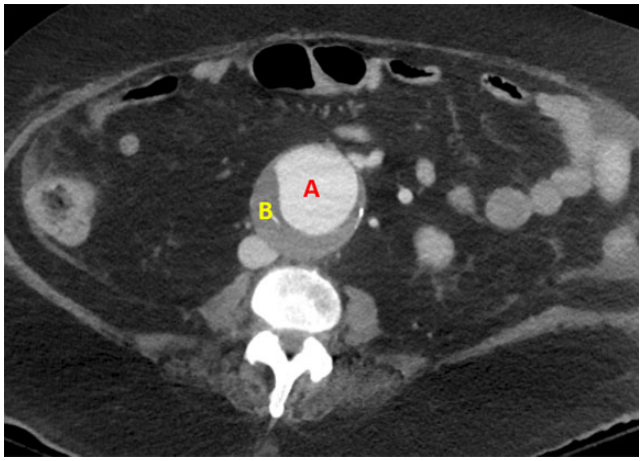

Figure 1. Abdominal CT image of the patient. A = Aortic lumen, highlighted by intravenous contrast material. B = Mural thrombus of aortic aneurysm. Computed tomography imaging was done with intravenous contrast material. Note the inferior vena cava (IVC) posterior and to the right of the mural thrombus. In a ruptured AAA, this would likely be obliterated. AAA indicates abdominal aortic aneurysm; CT computed tomography.

Diagnostic Findings, Part II

Figure 1 Depicts the CT findings for this patient. Describe the CT scan and your assessment for the next step in care of the patient.

The abdominal CT scan shows a widely dilated area of intravenously injected contrast material, revealing a widened aortic lumen. The mural thrombus can also be seen surrounding this contrast material. These 2 facts confirm an aortic aneurysm. The scan was taken distal to the renal arteries, therefore specifying the diagnosis to AAA. The peritoneal cavity does not contain any extravasation of contrast material, indicating an unruptured AAA. The SVS recommends elective surgical repair for aneurysms larger than 5.5 cm, and the figure caption notes that this aneurysm is 5.8 cm at maximum diameter. As such, this patient should likely undergo surgical repair of the AAA.

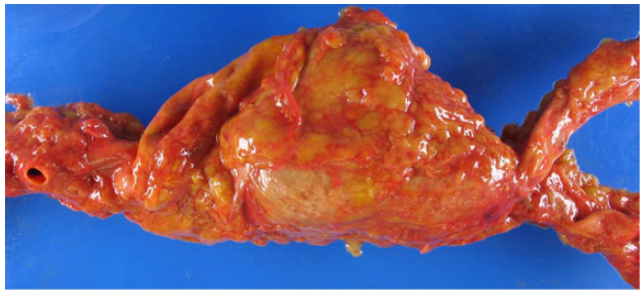

Figure 2. Gross anatomy of abdominal aortic aneurysm (AAA). Note the superior mesenteric artery superior (to the left in this image) to the aneurysm, and the bifurcation of the common iliac arteries inferiorly (to the right). Maximum diameter of aneurysm = 8.0 cm, well beyond the standard for surgical intervention.

Question/Discussion Points, Part II

What Clinical Sequelae Might Coincide With an Unruptured Abdominal Aortic Aneurysm?

Depending on the specific patient and aneurysm, an unruptured AAA may elicit a diverse set of clinical sequelae. For example, most patients with AAA are asymptomatic, and their aneurysms are discovered incidentally during physical examination or unrelated imaging.[4] For patients who are symptomatic—as the patient in this case—AAA may elicit abdominal or lower back pain, fever, syncope, a pulsatile mass in the abdomen or groin, and/or ischemia of the lower limb due to embolism.[4] However, these symptoms are not specific to AAA, and must be corroborated with imaging or further diagnostic testing. In essence, a patient with unruptured AAA may present with wide-ranging clinical sequelae depending on blood pressure, severity of atherosclerosis, and other confounding factors. If one patient has a stable AAA—for example, only 2.5 cm in diameter—clinical signs may be absent. Then again, if an aneurysm is large or aggressive, a patient might present with several of the characteristic symptoms.

Figure 2 Demonstrates the Gross Anatomy of an Unruptured AAA. Briefly Describe the Anatomy and its Clinical Implications.

Figure 2 shows an infrarenal, unruptured saccular AAA, in the classic location just superior to the common iliac bifurcation. A saccular aneurysm is one which bulges in a distinct, unilateral manner, creating a discrete pouch of dilated vascular wall. In contrast, fusiform aneurysms bulge circumferentially and are thus somewhat symmetrical. Both the saccular and fusiform types are "true" aneurysms because, unless ruptured, all 3 layers of the arterial wall remain intact (These layers are the intima, media, and adventitia.). Blood is therefore retained as a mural thrombus adherent to the arterial lumen, as opposed to in an extravascular hematoma.

The true aneurysm in Figure 2 is 8.0 cm in maximum diameter, making it a remarkably large aneurysm. Such an aneurysm would be at very high risk for rupture, likely necessitating surgical intervention. Some AAAs reach up to 20 cm in diameter, although this is uncommon.[2] An associated atherosclerotic plaque might obstruct blood flow to and through the iliac arteries, causing lower limb ischemia, which could also occur through thromboembolism.

Given the asymmetric, unilateral appearance of the referenced AAA, one might confuse this specimen for a "pseudoaneurysm." Pseudoaneurysms, like true aneurysms, result from defects in the vascular wall. However, there is a key difference between the two. In true aneurysms, all 3 layers of the arterial wall become dilated, creating an intravascular bulge that has the potential for rupture. On the other hand, pseudoaneurysms occur when blood ruptures through all 3 arterial layers but is contained within the extravascular tissue.[2] This forms an often asymmetrical hematoma outside the artery, still contiguous with the intravascular space. True aneurysms—until they rupture—retain blood completely within the intravascular space.

What Risk Factors Might Influence the Likelihood of Abdominal Aortic Aneurysm Rupture in This Patient?

Maximum AAA diameter is highly indicative of rupture risk. There is <1% yearly risk of rupture for aneurysms smaller than 3.9 cm in maximum diameter, increasing to 1% at 4.0 to 4.9 cm; 1% to 11% at 5.0 to 5.9 cm; 10% to 22% at 6.0 to 6.9 cm; and 30% to 33% at 7.0 cm or larger.[1,5] Rapid aneurysm expansion—defined as a baseline diameter increase of 5 mm or more over a 6-month period, or 10 mm over a 12-month period—also increases risk of rupture.[5] For comparison, the average rate of AAA expansion is approximately 2.6 mm per 12 months.[7] Larger aneurysms tend to expand faster than smaller ones, although expansion is nonlinear and can be quite stochastic.[8]

Other strong risk factors for rupture include tobacco use, hypertension, and female sex.[5,9] It is difficult to characterize the exact contributions of tobacco use, because the many components of tobacco smoke have wide-ranging, interrelated bioactivities *in vivo*. Nonetheless, studies suggest possible pathways in which T-cells and matrix-degrading enzymes cause inflammatory damage to the aortic SMCs and ECM, while also reducing expression of enzymes such as prolyl-4-hydroxylase.[3] These enzymes are critical to collagen synthesis, and their suppression might inhibit repair of aortic tissue. As the aortic tissue incurs further damage and is unable to repair itself, aneurysmal dilation can continue up to rupture.

Studies indicate that females with AAA are more likely than males to suffer from AAA rupture—regardless of aneurysm size interval—with a 4-fold greater risk of rupture in aneurysms less than 5.5 cm wide.[10] Obviously, this does not impact the present patient, but the discrepancy is important to consider nonetheless. Some explanation may be found in the sex-neutral practices of AAA management and classification. For example, the SVS currently recommends observation for asymptomatic aneurysms <5.5 cm in diameter, regardless of patient sex.[5] However, studies also suggest that females have smaller relative aortic diameters, indicating that if a female and a male of similar size have AAAs of equal diameter, the female has undergone a greater

proportional dilation of the aneurysm.[11] Therefore, female patients with aneurysm diameters of 5.5 cm may exceed the proper minimum threshold for recommendation of elective surgery. This means that females may incur greater risk of AAA rupture, because their current sex-neutral thresholds for elective surgical intervention are too high.

Finally, uncontrolled hypertension can increase risk of AAA rupture—although the relationship between hypertension and AAA expansion is less clear—as high blood pressures propagate stress upon an already-dilated arterial wall.[1] In order to prevent further damage to the aorta, initial treatment of AAA typically involves antihypertensive medication.

The present patient—given his history of smoking, hypertension, and aneurysm size—is certainly at high risk of AAA rupture. Rupture carries significant potential for mortality, and the patient should thus be carefully monitored and treated moving forward.

Discuss the Mortality Rates Associated With Ruptured Abdominal Aortic Aneurysm

A ruptured AAA is a serious, often fatal surgical emergency. Upon rupture, patients can present with 3 major symptoms: pain, pulsatile mass, and hypotension. However, less than half of patients will present with all three. This can lead to misdiagnosis, contributing to the 90% overall mortality rate in AAA.[12] There are 4 main sites for AAA rupture—intraperitoneal, retroperitoneal, aortocaval fistula, and primary aortoduodenal fistula—and each one presents with distinct and nuanced clinical features.[12]

If This Patient Suffered From a Ruptured Abdominal Aortic Aneurysm, How Might His Computed Tomography Scan Differ From the Original?

One would expect extravasation of the contrast material, leading to visible retroperitoneal hematoma and loss of the fat plane between the aorta and its surrounding tissue. In symptomatic but unruptured AAA, the CT often reveals several distinct findings in lieu of such extravasation: irregular aortic wall, draping of the aorta over vertebral bodies, and/or the crescent shape of a layering hematoma.[4]

Figure 3 Presents the CT Scan From a Different Patient. Describe the Figure and Diagnose This New Patient.

In Figure 3A, we see a dilated aortic lumen, with high density of blood in lieu of the periaortic fat plane. This blood appears to have dissected into the retroperitoneum and obliterated the fat plane around the inferior vena cava (IVC) and right psoas muscle. Figure 3B shows a colored version of the same scan, giving appreciation of the acute blood density surrounding the periaortic fat plane, obliterated IVC, retroperitoneum, and psoas muscle. These images are consistent with a ruptured AAA, as the extravasation almost certainly originated from an aneurysm directly adjacent to this abdominal region.

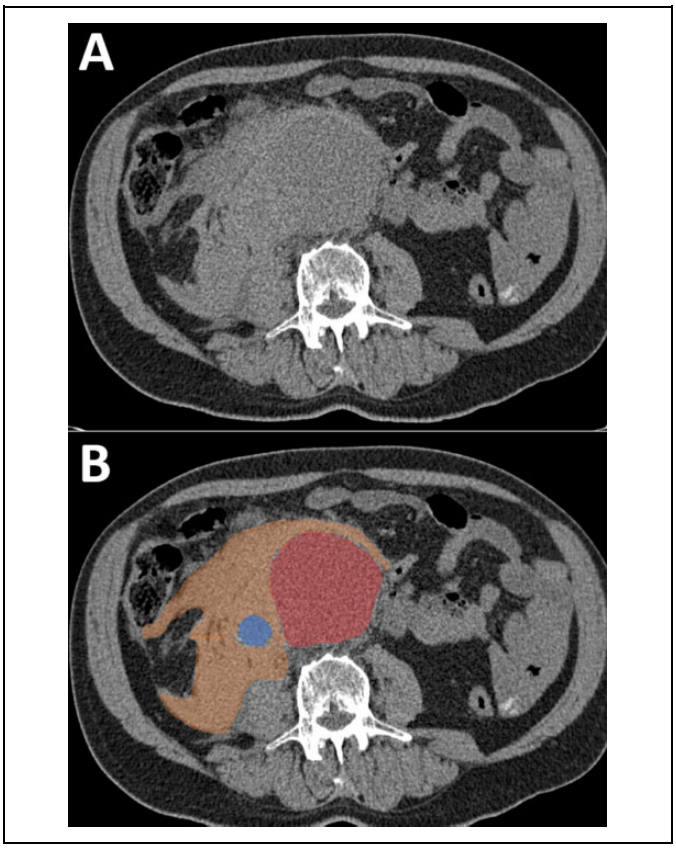

Figure 3. Abdominal computed tomography image of a ruptured AAA (A) alongside the same image where the dilated aorta is highlighted in red, the inferior vena cava in blue, and hemorrhage in orange (B). Maximum aneurysm diameter = 5.8 cm. Computed tomography imaging was done with intravenous contrast material. AAA indicates abdominal aortic aneurysm.

Compare and Contrast the Etiology, Clinical Description, Risk Factors, and Epidemiology of Aortic Aneurysm and Aortic Dissection

An aortic aneurysm involves dilation of all 3 layers of the arterial wall—the intima, the media, and the adventitia. In contrast, AD occurs when blood enters the aortic wall through an intimal tear and then dissects progressively through the media.[13] A "dissection" then continues as blood pulses through the tissue plane, splitting the attenuated media. Histological data from ADs contrast starkly with those of normal aortic specimens. For instance, Figure 4A depicts a normal, healthy media identified by numerous elastin fibers colored black by the Elastic Van Gieson (EVG) stain. (EVG forms a variety of strong bonds with elastin, staining the elastic fibers black. As such, EVG is typically used to visualize normal or pathologic elastic fibers.) In contrast, Figure 4B depicts a medial layer split by dissecting blood, alongside atherosclerosis between the intima and attenuated media. The pathological term for this attenuation of the media is *cystic medial necrosis*.

Aortic dissection is therefore characterized by a proximal intimal tear—such as in the ascending aorta—and a medial

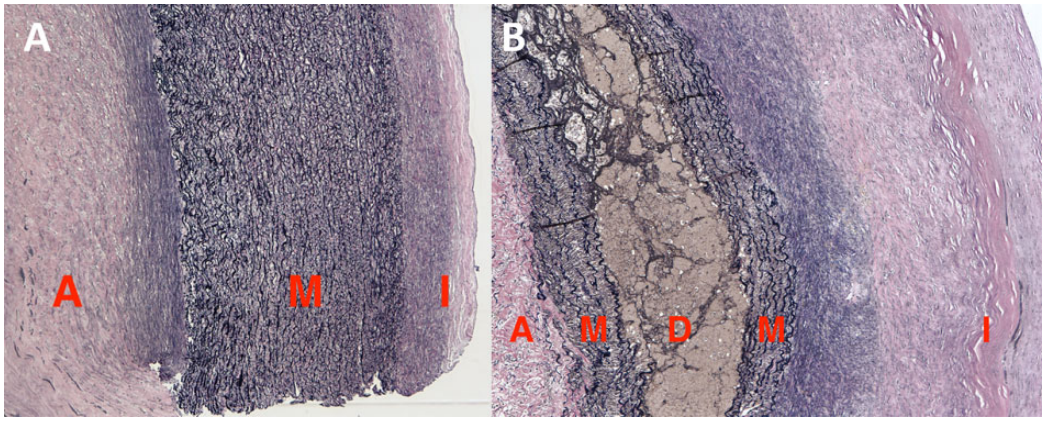

Figure 4. Photomicrograph of normal aorta with intact, elastic fibers of tunica media (A), contrasted with photomicrograph of blood dissecting through attenuated and weakened tunica media (B). Photomicrographs were taken with EVG stain and at 40× magnification. Note how in the dissection specimen, the tunica intima is thickened with an atherosclerotic plaque. A = tunica adventitia; M = tunica media; D = dissecting blood; I = tunica intima. EVG indicates Elastic Van Gieson.

dissection which can proceed quite distally. This dissection need not involve the adventitia. Nonetheless, adventitial rupture can still occur, necessitating immediate emergency action.

Both AD and aortic aneurysm result from some form of structural vascular weakening in the SMCs and ECM. However, there are distinct differences between the two, beginning with clinical presentation. In AD, patients typically present with a "tearing" pain which begins in the chest and then radiates toward the back.[13] This symptom is often very acute, with 85% of patients describing a sudden onset of unique, piercing, and severe pain. The pain can also migrate to the abdomen as dissection progresses. Syncope presents in 5% to 10% of acute patients, while a pulse deficit occurs in 9% to 30% of thoracic dissections. If a dissection progresses proximally from the ascending aorta to the aortic valve, a heart murmur can also be heard due to aortic valve regurgitation. These clinical signs may vary depending on the site—or type, as mentioned below—of a given AD.

The Stanford classification system names 2 categories for AD: type A and type B. Type A dissections involve the ascending aorta, and may involve the aortic arch or descending aorta. Type B dissections begin distal to the ascending aorta. Ascending dissections occur nearly twice as often as descending dissections, and isolated abdominal dissections are not regularly reported.[13] Aortic dissections are also classified as acute (symptomatic for 2 weeks or less) or chronic (symptomatic for more than 2 weeks).

High blood pressure is the most prominent risk factor for AD, with 1 review finding that over 70% of acute patients have an antecedent history of hypertension.[2,14] Preexisting aneurysms increase risk of AD, being present in over 20% of patients with descending dissections and over 12% of patients with ascending dissections.[13] Family history, male sex, congenital connective tissue disorders, and advanced age can also increase risk for the disease.[13,14] For instance, one review found that over 50% of AD patients younger than 40 years also suffered from Marfan Syndrome, compared to 2% in those older than 40 years.[14] The same review indicated that those with a bicuspid aortic valve are at 9 times greater risk of the disease. Few studies exist to suggest any racial or ethnic predisposition to AD. In the United States, estimated incidence ranges from 2.6 to 3.5 cases per 100 000 person-years, with a mortality rate of 25% to 30%.[13]

Aortic aneurysms, like dissections, are diverse and can occur along any point of the aorta. Because this case is concerned with AAA—and because AAA is the most common form of aortic aneurysm—the clinical sequelae alluded to earlier will suffice for clinical comparisons with AD. However, it is important to reiterate that most patients with AAA do not present with any symptoms and that their aneurysms are discovered incidentally or after rupture.[4] Given the aforementioned classifications of AD, it may also help to reference the various classes of AAA mentioned earlier—saccular versus fusiform, true aneurysm versus pseudoaneurysm, and ruptured versus unruptured.

Hypertension is thought to contribute to the onset and/or rupture of some aortic anuerysms.[2,15] Other predisposing factors for aortic aneurysm include atherosclerotic disease, preexisting aneurysms outside the aorta (given that atherosclerosis is a systemic disease), obesity, smoking, and high salt intake.[16] Certain inherited connective tissue disorders, such as Marfan Syndrome, can lead to aortic aneurysm by weakening the ECM and/or SMCs and decreasing structural integrity of the arterial wall.[1,13] However, such diseases are rare. Advanced age and caucasian ethnicity are more likely risk factors: Males between 65 to 80 years of age face up to 6 times higher risk of AAA development than their female counterparts, and caucasian populations have the highest rates of AAA in the United States—up to 10-fold higher than Asian American populations and twice as high as African American groups.[1] In Western countries, the incidence of AAA is approximately 2.5 to 6.5 cases per 1000 person-years, with a prevalence of 4% to 8% based on screening studies.[1] The incidence of AAA rupture is much lower, with one Swedish study suggesting a rate of 11 cases per 100 000 person-years.[17]

In essence, AD and aortic aneurysm both involve (1) a weakening or degradation of SMCs or ECM in the arterial

Table 1. Comparison of Abdominal Aortic Aneurysm and Aortic Dissection.

	Abdominal Aortic Aneurysm		
	Unruptured but Symptomatic	Ruptured	Aortic Dissection
Etiology	Weakening and degradation of SMCs and ECM in arterial wall Dilation of all 3 vascular layers (true aneurysms), leading to saccular or fusiform dilation of aorta	Continued SMC and ECM degradation further weakens arterial wall Aneurysm expands, as arterial wall loses elasticity and compliance Weakened, stiffened wall ruptures	Weakening and degradation of SMCs and ECM in arterial wall Intimal tear, leading to blood dissecting through attenuated media As blood continues to pulse through aorta, dissection often progresses distally
Clinical descriptions	Pain in abdomen, back, and/or flank Palpable mass in abdomen Lower limb ischemia Presyncope or brief episodes of syncope Fever, malaise	Excruciating pain in abdomen, back, and/or flank Hypotension Palpable, pulsatile mass in abdomen Syncope Tachycardia	Sudden, excruciating, stabbing pain Pain usually located in chest, radiating to back Pulse deficit Syncope Heart murmur due to aortic valve regurgitation
Risk factors	Atherosclerosis Smoking history Advanced age Hypertension Preexisting nonaortic aneurysms Connective tissue disorders (eg, Marfan syndrome) Male sex Caucasian race	Large aneurysm diameter Rapid aneurysm expansion rate Female sex Hypertension Smoking history Atherosclerosis	Hypertension Preexisting aneurysms Connective tissue disorders (eg, Marfan syndrome) Bicuspid aortic valve Male sex
Epidemiology in Western countries	Incidence: 2.5-6.5 per 1000 person-years[1] Prevalence: 4%-8% based on screening data[1]	Incidence: approx. 11 per 100 000 person-years[17] Mortality rate: approx. 90%[12]	Incidence: 2.6-3.5 per 100 000 person-years[13] Mortality rate: 25%-30%[13]

Abbreviations: approx, approximately; ECM, extracellular matrix; SMCs, smooth muscle cells.

wall, (2) potential for rupture, which carries high mortality rates, and (3) hypertension as a risk factor, alongside existing aneurysms, advanced age, and inherited connective tissue disorders.

At the same time, differences between the two include (1) their effects on the intima, media, and adventitia of the arterial wall, (2) their various clinical presentations described above, (3) their systems of classification and categorization, and (4) their presence—or lack thereof—of ethnic, racial, and/or sex-based dispositions.

There are numerous other comparisons to be made based on dissection type, aneurysm classification, and other factors. Table 1 broadly summarizes the similarities and differences between AAA and AD.

Teaching Points

- Although most AAA cases are asymptomatic, clinical features include abdominal and/or back pain, pulsatile masses, nausea, presyncope or brief episodes of syncope, and lower-limb ischemia.
- True aneurysms involve dilation of the intima, media, and adventitia and can be fusiform or saccular.
- Risk factors for AAA development include atherosclerosis, hypertension, smoking, male sex, advanced age, presence of other non-aortic aneurysms, and caucasian race.
- Atherosclerosis and hypertension are particularly important to the etiology of AAA.
- Abdominal aortic aneurysm rupture carries a 90% mortality rate and should always be ruled out in patients suspected of AAA.
- Risk factors for AAA rupture include large aneurysm diameter, atherosclerosis, rapid aneurysm expansion, tobacco use, hypertension, and female sex.
- In AD, blood enters through an intimal tear and dissects through the media, without necessarily involving the adventitia.
- Clinical features of AD may include sudden radiating chest pain, pulse deficit, syncope, and heart murmur due to aortic valve regurgitation.
- In pseudoaneurysms, blood ruptures through all 3 arterial layers but is contained within extravascular tissue.
- In the Stanford classification system, type A aortic dissections involve the ascending aorta, while type B dissections begin distal to the ascending aorta.

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Declaration of Conflicting Interests

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Educational Case: Fibroadenoma of the Breast

H. James Williams, MD[1]

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, disease mechanisms, breast, neoplasia, fibroadenoma, palpable breast lesion, mammographic findings, phyllodes tumor

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Primary Objective

Objective BR2.1: Fibroadenoma and Phyllodes Tumor. Compare and contrast fibroadenoma and phyllodes tumor in terms of clinical features, morphologic findings, and prognosis.

Competency 2: Organ System Pathology; Topic BR: Breast; Learning Goal 2: Molecular Basis of Breast Neoplasms.

Secondary Objective

Objective N3.1: Morphologic Features of Neoplasia. Describe the essential morphologic features of neoplasms and indicate how these can be used to diagnose, classify, and predict biological behavior of cancers.

Competency 1: Disease Mechanisms and Processes; Topic N: Neoplasia; Learning Goal 3: Characteristics of Neoplasia.

Patient Presentation

A 37-year-old woman presents to her physician with concern about a left breast nodule she recently discovered on self-examination. The patient states that the nodule is approximately 2 cm in size, close to her left axilla, and feels firm. She is concerned because her mother, age 54, was recently diagnosed with breast cancer.

Questions/Discussion Points, Part 1

What Pertinent Questions Should be Asked as Part of the Detailed History Prior to Physical Examination?

How long has the nodule been there? If the lesion developed very recently, one could choose to follow the lesion for a short time to see if it persists.

Has it changed in size over time? Change in size could include decreasing, increasing, or fluctuating lesions. Fluctuation in size would be suggestive of menstrual effect or fibrocystic change. A decrease in size might indicate a cyst getting smaller. An increase in size would be more worrisome for a more serious lesion.

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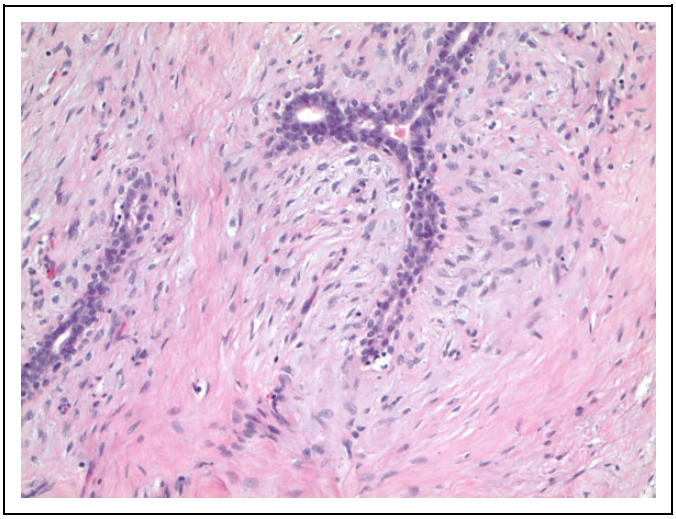

Figure 3. Microscopic image of left breast nodule at high power, H&E 20×. The stroma of the lesion has low cellularity with no mitoses or cytologic atypia. The epithelial component shows bland cytologic features with associated myoepithelial cells.

Is the nodule painful? Malignancies are not typically painful; however, inflammatory lesions can be painful as could benign lesions.

Has there been nipple discharge and if so, is it bloody? Bloody nipple discharge may be associated with an intraductal papilloma or, more rarely, cancer. A finding of nipple discharge would need to be investigated more carefully.

Does anyone in your family have or have had breast cancer? If there is a family history of breast cancer, what is the relationship of the family member with the patient (ie, is it the patient's mother, sister, or daughter)? Also, what was the age at time of diagnosis of the family member? Younger age of breast cancer would be much more concerning for a possible familiar component of a breast cancer than breast cancer in an older first-degree relative. This question is addressing the associated increased risk of malignancy and/or hereditary disease in close relatives, especially if they developed breast cancer at a young age.

On physical examination of the patient's left breast, what findings would favor either a benign or malignant diagnosis? Physical examination can be helpful, as some features are more common with benign or malignant lesions. Features of benign neoplasms include the following: multiple indistinct nodules (lumpy breast) that favor fibrocystic changes and lesions beneath the nipple which may suggest an intraductal papilloma.

However, a fixed, irregular, and firm mass is suspicious for malignancy as is dimpling of the overlying skin. Another important factor is location of the lesion within the breast, as 50% of breast cancers arise in the upper outer quadrant; thus, lesions in this area would be more suspicious for malignancy.

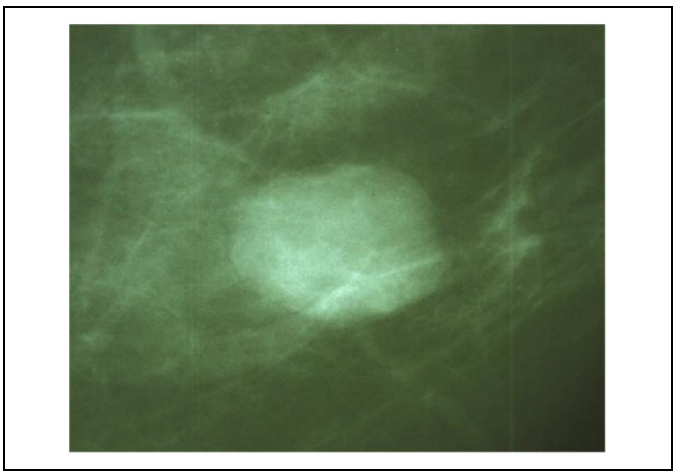

Figure 1. Mammogram of left breast nodule. The lesion is homogeneous and is sharply demarcated from the normal breast tissue.

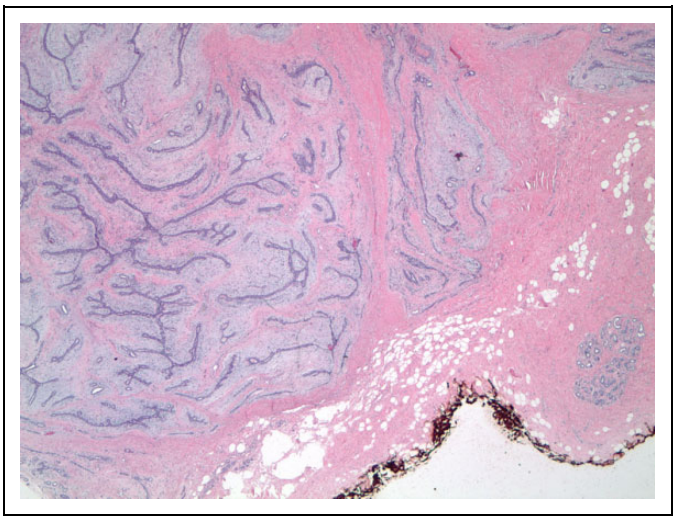

Figure 2. Microscopic image of left breast nodule at low power, H&E 2×. On low power, the lesion is seen to be sharply demarcated from the adjacent normal breast tissue.

Diagnostic Findings, Part 2

The patient undergoes mammography of the left breast nodule. The mammography is shown in Figure 1.

Questions/Discussion Points, Part 2

What Radiographic Findings in Figure 1 Are Seen, and Do They Favor a Benign or Malignant Diagnosis?

Similar to physical examination, radiologic examination is important in working up breast lesions. Several factors are more suggestive of benign versus malignant lesions. The following findings favor a benign process when they

are present: sharp distinct borders, homogenous texture, and ovoid shape. The following factors favor malignant when they are present: stellate infiltrative borders, heterogenous texture, round shape, and presence of coarse calcifications.

In the mammographic image for the patient, a round homogenous lesion is seen. This would favor a benign process. Confirmation of the imaging impression requires histologic examination of the lesion either by biopsy of the lesion or by conservative excision.

Diagnostic Findings, Part 3

The breast nodule is excised and sent for pathologic examination (see Figures 2 and 3).

Questions/Discussion Points, Part 3

What are the Pertinent Histologic Findings Seen in Figures 2 and 3?

On low-power image of the breast biospy, as seen in Figure 2, the lesion is seen to be sharply demarcated from the adjacent normal breast tissue. This is suggestive of a benign process. When looking at higher power in Figure 3, there is a predominance of stromal tissue with compression of the epithelial component. The stroma is of low cellularity with no mitoses or cytologic atypia seen. In addition, the epithelial component shows bland cytologic features with associated myoepithelial cells.

What Is Your Diagnosis?

Fibroadenoma of the breast.

Discuss the Clinical Features and Pathophysiology of Fibroadenomas and What Is the Prognosis and Management for This Lesion?

Fibroadenomas are the most common benign breast neoplasms and typically present in women 20 to 35 years old.[1] The tumors are usually solitary but may be multiple (20%). Clinically, they may be detected by the patient or the physician on breast examination as a well-demarcated, freely mobile, firm mass that is usually <3 cm in diameter. The fibroadenoma is a neoplasm of the specialized lobular stroma with typically low cellularity, no cytologic atypia, and mitotic figures absent or rare. The associated benign epithelium has associated myoepithelial cells and may have an intracanalicular or pericanalicular pattern.[2] The radiographic appearance of fibroadenoma characteristically shows an ovoid homogenous mass with sharp distinct borders.

Patients with fibroadenomas are associated with a slight increased risk of breast cancer, particularly when there are proliferative fibrocystic changes involving the tumor. As would be anticipated, fibroadenomas are hormonally responsive (may enlarge during pregnancy and reduce in size in postmenopause).

As the fibroadenoma is a benign tumor, in the appropriate clinicoradiographic setting, once the tumor is diagnosed by fine-needle aspiration or needle core biopsy, it may be safely followed. If the tumor is a cosmetic problem or if preferred by the patient, conservative excision can be performed.[3]

Discuss a Common Tumor in the Differential Diagnosis of a Fibroadenoma

The histologic differential diagnosis includes the phyllodes tumor in which there is increased cellularity of the stroma, and the epithelial component demonstrates a "leaf-like" architectural pattern.[1] Low-grade phyllodes tumors have these features with mild cytologic atypia and occasional mitoses. High-grade phyllodes tumors in addition to the increased stromal cellularity have marked cytologic atypia and increased mitoses, some of which may be atypical. Because of the higher risk of recurrences, wide excision is indicated for phyllodes tumors. In addition to the risk of recurrences, the high-grade phyllodes tumor has the potential to metastasize.

Teaching Points

- Benign features include the following: Multiple indistinct nodules (lumpy breast) favors fibrocystic changes, and lesions beneath the nipple may suggest a papilloma.
- A fixed irregular firm mass on physical examination is suspicious for malignancy, as is dimpling of the overlying skin.
- On radiography, a benign process tends to have sharp distinct borders, homogenous texture, and ovoid shape.
- Fibroadenomas are the most common benign breast neoplasms and typically present in women 20 to 35 years old.
- The fibroadenoma is a neoplasm of the specialized lobular stroma with typically low cellularity, no cytologic atypia, and mitotic figures absent or rare. The associated benign epithelium has associated myoepithelial cells and may have an intracanalicular or pericanalicular pattern.
- The phyllodes tumor has increased cellularity of the stroma, and the epithelial component demonstrates a "leaf-like" architectural pattern. Low-grade phyllodes tumors may have mild cytologic atypia and occasional mitoses. High-grade phyllodes tumors, in addition to the increased stromal cellularity, have marked cytologic atypia and increased mitoses, some of which may be atypical.

Declaration of Conflicting Interests

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Educational Case: Wilms Tumor

Alison R. Huppmann, MD[1]

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, kidney, renal neoplasia, Wilms tumor, pediatric, syndrome

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Primary Objective

Objective UTK1.4: Wilms Tumor. Describe the clinical and pathologic features and molecular basis for Wilms tumor and list the histologic features that are important to recognize in determining prognosis, and the etiology of Wilms tumor as part of different syndromes.

Competency 2: Organ System Pathology; Topic UTK: Kidney; Learning Goal 1: Renal Neoplasia.

Patient Presentation

A 2-year-old boy presents to his pediatrician after his mother noticed a "lump in his belly." Further questioning reveals only that the patient has seemed slightly more tired lately. He has a history of a urinary tract malformation that required surgical repair. Family history is negative for malignancy or major medical problems. Physical examination reveals a blood pressure of 142/94 mm Hg with other vital signs within normal limits. A large mass is palpable in the abdomen and appears to be centered on the right side.

Diagnostic Findings

An abdominal ultrasound shows a solid mass in the right abdomen. A computed tomography (CT) scan discloses a mass arising from the right kidney (Figure 1). A nephrectomy is performed.

Questions/Discussion Points

Which Entities May Present as an Abdominal Mass in a Child? Include Both Neoplastic and Nonneoplastic Lesions

For abdominal masses occurring at birth or within the first few years of life, congenital anomalies are a strong consideration, including gastrointestinal tract duplications, cysts arising from the omentum or mesentery, cysts of the hepatobiliary system, intussusception, and genitourinary tract anomalies such as polycystic or hydronephrotic kidneys or an enlarged bladder. Splenomegaly or hepatomegaly, for any reason, may present as a mass. If trauma is an antecedent factor, the cause may be a hematoma or pancreatic pseudocyst. An intra-abdominal abscess, most commonly arising from the appendix, is another benign cause. Malignant tumors can also occur in the abdomen, including neuroblastoma, Wilms tumor, hepatoblastoma, germ

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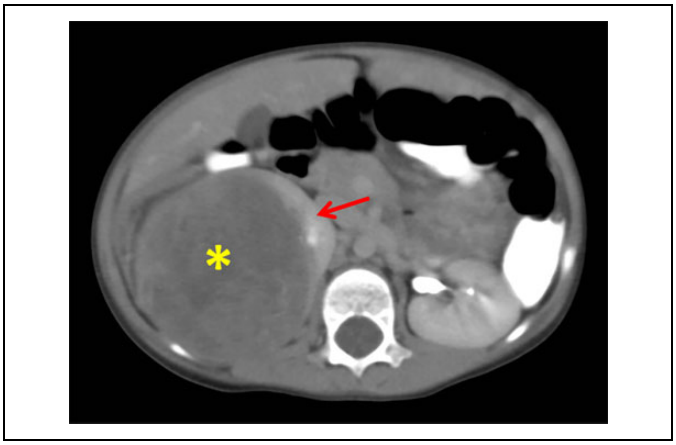

Figure 1. A computed tomography (CT) scan shows a large mass (*) on the right side with the remaining kidney (arrow) showing the "claw sign" around the mass, indicating that is likely of renal origin.

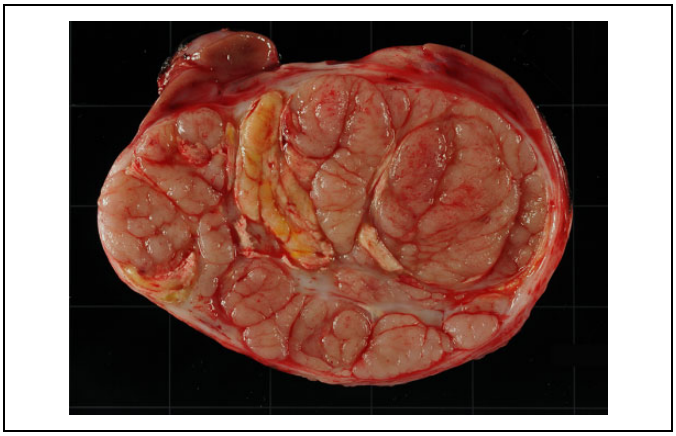

Figure 2. Grossly, a large, tan, well-circumscribed, encapsulated mass has replaced much of the normal renal parenchyma. Yellow discoloration indicates areas of necrosis.

cell tumors, sarcomas (eg, rhabdomyosarcoma), and rarely lymphomas.[1]

Describe the Gross and Histologic Features in Figures 2-4. Based on the Clinical and Pathologic Features, What Is Your Diagnosis?

Grossly, a large, tan, fleshy, well-circumscribed mass replaces most of the renal parenchyma (Figure 2). Foci of yellow discoloration indicate necrosis. A capsule surrounds the periphery of the mass. Areas of hemorrhage and/or cystic change can be seen in some cases. The low-power histologic image (Figure 3) demonstrates a variable appearance due to several different components of the tumor. A higher power view (Figure 4) allows closer examination of these varied elements, showing a mixture of immature tubules, small round blue cells, and spindled cells. These findings are consistent with a diagnosis of Wilms tumor (nephroblastoma).

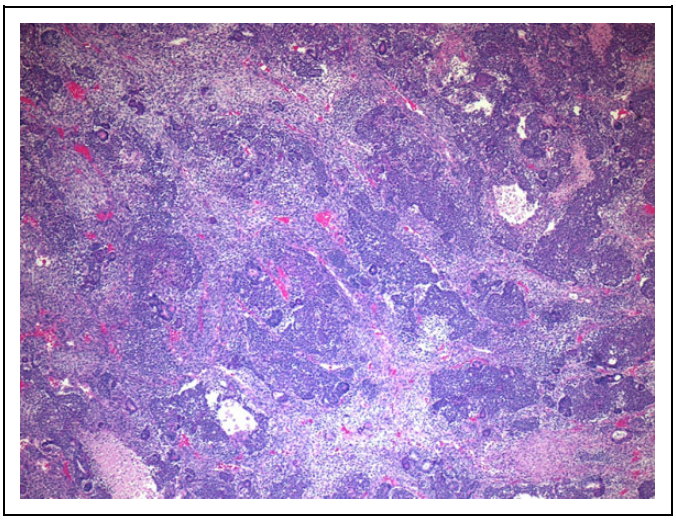

Figure 3. On low power magnification of the mass, the histology shows a variable appearance due to the different elements composing the tumor (hematoxylin and eosin, ×40).

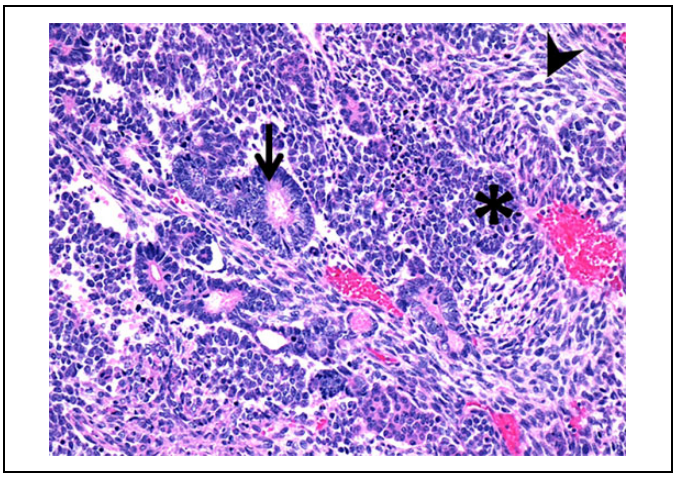

Figure 4. At intermediate magnification, primitive tubules (arrow), small round blue cells (*), and spindled cells (arrowhead) represent epithelial, blastemal, and stromal components, respectively (hematoxylin and eosin, ×200).

Like some other pediatric tumors, the histology of Wilms tumor appears similar to primitive (embryonic or fetal) elements that would have been present in the tissue of origination, in this case the kidney (Figure 5). A classic Wilms tumor is triphasic, with epithelial, blastemal, and stromal elements; although any one of these 3 may predominate in a given tumor. Immature tubules and glomeruli compose the epithelial areas. The blastemal cells are undifferentiated-appearing small blue cells. Stromal cells are usually spindled with a fibrotic or myxoid background, and heterologous differentiation (skeletal muscle, cartilage, osteoid, etc) can be found in some cases (not seen in these images).[2]

Wilms tumor is the most common primary renal malignancy of childhood.[2] Other primary renal tumors of childhood include

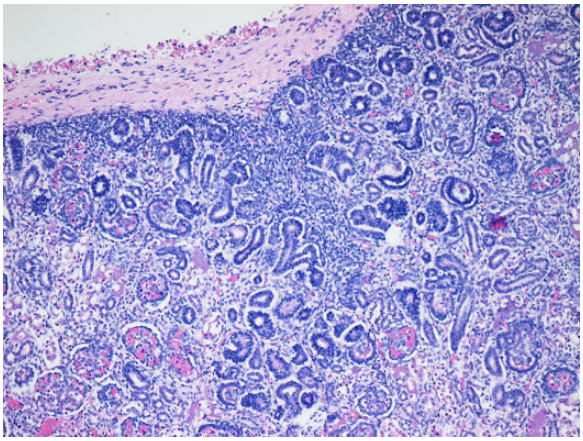

Figure 5. This is the histologic appearance of fetal renal cortex at 19 weeks' gestation. Note the nephrogenic zone in the subcapsular area and its histologic similarity to Wilms tumor, with primitive glomeruli, tubules, and blastema (hematoxylin and eosin, ×100). The nephrogenic zone should disappear by approximately 36 weeks' gestation.

mesoblastic nephroma, clear cell sarcoma of the kidney, rhabdoid tumor of the kidney, and, in adolescents, renal cell carcinoma. These tumors do not contain the triphasic elements seen in Wilms tumors.

What Is the Typical Clinical Presentation of a Wilms Tumor?

Wilms tumor most commonly occurs in young children between age 2 and 5. However, older children and even adults can be affected. The most common presentation is an abdominal mass. These are often identified by a caregiver while bathing or changing the child's clothes or by a physician on routine physical examination. Other frequent signs and symptoms include hypertension, abdominal pain, fever, painless hematuria, and anemia.[3]

What Other Tumors Are Included in the Category of "Small Round Blue Cells Tumors"? How Are These Differentiated?

Small round blue cell tumors are those composed of cells with scant cytoplasm, so that the tumor appears "blue" (basophilic) from low power since the nuclei dominate the histology. Tumors commonly included in this group are leukemia/lymphoma, neuroblastoma, Wilms tumor, rhabdomyosarcoma, Ewing sarcoma family of tumors, desmoplastic small round cell tumor, rhabdoid tumor, and other undifferentiated types of sarcoma. Note that most of these tumor types are more common in children. Many of the small round blue cell tumors of childhood show histological features that permit a preliminary diagnosis. Panels of immunohistochemical stains and genetic or molecular testing are useful to confirm the findings.

What Are Nephrogenic Rests? What Is Their Significance?

Nephrogenic rests are nonencapsulated areas of persistent immature renal tissue with histologic features that can resemble Wilms tumor. These rests usually regress or differentiate, but they can become malignant if they persist. Evidence supporting this theory includes shared genetic alterations with rests and tumor in the same patient.[2] Although seen in 1% of the general population,[3] nephrogenic rests are identified in the adjacent renal parenchyma of up to 40% of patients with unilateral tumors and almost 100% of bilateral tumors. These rests are important to identify, as they imply an increased risk of Wilms tumor in the contralateral kidney, necessitating close monitoring of the patient.[2]

Which Patient Characteristics Might Lead You to Suspect an Associated Syndrome in a Pediatric Patient With Cancer? Which Congenital Syndromes Are Most Often Associated With Wilms Tumor?

The possibility of a syndrome should be considered in any pediatric oncology patient with a personal or family history of malformation(s), personal or family history of malignancy, early onset of cancer, certain physical characteristics, or rare forms of cancer. Approximately 10% of Wilms tumors occur in patients with congenital syndromes. Those most commonly associated are WAGR syndrome (*W*ilms tumor, *a*niridia, *g*enital anomalies, mental *r*etardation), Denys-Drash syndrome (renal mesangial sclerosis, early-onset renal failure, gonadal dysgenesis), and Beckwith-Wiedemann syndrome (hemihypertrophy, organomegaly, macroglossia, and omphalocele). A large number of other syndromes are less commonly associated.[2]

Describe Some of the Common Genetic Changes Associated With Wilms Tumor

Genetic mutation(s) have been identified in one-third of Wilms tumors as yet. Some of these have been found due to their association with the congenital syndromes that convey an increased risk of Wilms tumor. Both WAGR and Denys-Drash syndromes are associated with mutations in the *WT1* gene, although due to a deletion in WAGR and a missense mutation in Denys-Drash. *WT1* is a tumor suppressor gene and encodes for a transcription factor that plays a critical role in development of the kidneys and gonads. The homozygous *WT1* mutations detected in Wilms tumors lead to loss of function.[2]

Beckwith-Wiedemann syndrome is associated with alterations in chromosome 11p15.5. One of the genes in this region, *IGF2*, is normally imprinted, with expression only by the paternal allele. Either loss of imprinting or uniparental disomy of *IGF2* has been identified in some Wilms tumors.[2]

CTNNB1 encodes for β-catenin, a key regulator of the Wnt signaling pathway. Mutations in *CTNNB1* are identified in 10% to 15% of Wilms tumors. Another gene associated with the

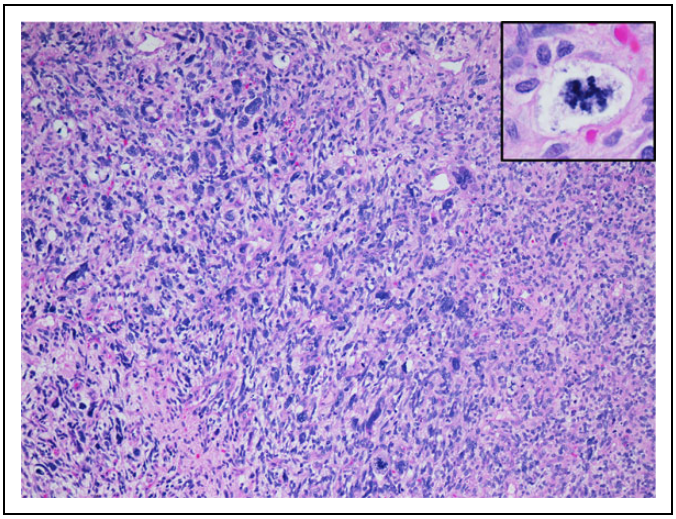

Figure 6. This tumor contains scattered cells with hyperchromatic nuclei that are much larger than the other nuclei. The inset shows an atypical mitotic figure. These findings indicate anaplasia (hematoxylin and eosin, ×100; inset, ×1000).

same pathway, *WTX*, is mutated in some tumors; *TP53* mutations are even less frequent. Many other less frequent genetic mutations have been identified, either alone or in combination with those previously discussed.[3]

What Histological Feature in Wilms Tumor Is Considered to be Unfavorable?

The feature in Wilms tumor indicative of unfavorable histology is anaplasia. This is shown in Figure 6. Anaplasia in Wilms tumor is defined as the presence of cells with large hyperchromatic nuclei (generally at least 3 times the size of adjacent nonanaplastic nuclei) and the presence of abnormal, polyploid mitotic figures. It is seen in 5% to 10% of Wilms tumors. As a diffuse finding, anaplasia is associated with resistance to chemotherapy and conveys a poorer prognosis in advanced-stage disease. It is linked to *TP53* mutations.[4]

Where Is Wilms Tumor Most Likely to Spread?

Renal vein extension is common. Noncontiguous spread goes to the regional lymph nodes, with the lungs being the most common site of distant metastasis.

What Other Factors Affect Prognosis in Wilms Tumor?

Tumor histology is possibly the most critical factor affecting prognosis, but other aspects considered include tumor stage, patient age, loss of heterozygosity (LOH) for chromosomes 1p and 16q, tumor weight, and completeness of lung nodule response. Briefly, staging for Wilms tumors is as follows: stage I—tumor confined to the kidney and removed completely by surgery; stage II—tumor extends beyond the kidney but is completely removed by surgery; stage III—tumor remains in the patient after surgery but is confined to the abdomen; stage IV—hematogenous metastases to lungs, liver, lymph nodes outside the abdomen, and so on; stage V—bilateral tumors at diagnosis. Notably, if a biopsy is performed prior to resection, the patient is automatically at least Stage III, which is why biopsy is not often utilized for pediatric renal tumors.[4]

Current treatment includes surgery and chemotherapy with or without radiation. The last 50 years have shown a dramatic improvement in prognosis for patients with Wilms tumor, with a current cure rate of approximately 90%.[4]

Teaching Points

- Wilms tumor is the most common primary renal tumor of childhood, most commonly presenting as an abdominal mass in a child 2 to 5 years of age.
- Many benign and malignant conditions can present as an abdominal mass in a child, necessitating a complete evaluation of the patient to arrive at the correct diagnosis.
- Genetic changes involved in the pathogenesis of Wilms tumor include the *WT1* gene and chromosome 11p15.5. These were partly identified through their association with some of the congenital syndromes with an increased risk of Wilms tumor, WAGR, Denys-Drash, and Beckwith-Wiedemann syndromes.
- An associated congenital syndrome should be suspected in a pediatric oncology patient with a personal or family history of a malformation or malignancy.
- A classic Wilms tumor has triphasic histology, including epithelial, blastemal, and stromal elements. Nephrogenic rests are presumed precursors to Wilms tumor and can have similar histologic features, although they are not encapsulated.
- Small round blue cells tumors have a similar histologic appearance of small cells with scant cytoplasm. Many of these tumors occur in childhood and include Wilms tumor, neuroblastoma, leukemia/lymphoma, rhabdomyosarcoma, and Ewing sarcoma family of tumors.
- Histology is a key predictor of prognosis in Wilms tumor, as anaplasia is associated with a less favorable prognosis. Other prognostic markers include age, stage, LOH 1p and 16q, tumor weight, and responsiveness of lung metastases.

Author's Note

The opinions expressed herein are those of the author and are not necessarily representative of those of the Uniformed Services University of the Health Sciences (USUHS), the Department of Defense (DOD), or the United States Army, Navy, or Air Force.

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Educational Case: Pheochromocytoma

Clinton Westover, MD[1] and Richard Michael Conran, MD, PhD, JD[1]

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, endocrine, pheochromocytoma, paraganglioma, adrenal tumor, multiple endocrine neoplasia, secondary hypertension, familial pheochromocytoma-paraganglioma syndrome

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Primary Objective

EN5.3: Pheochromocytoma and Paraganglioma: Outline the clinicopathologic features of pheochromocytoma and compare and contrast the hereditary cancer syndromes associated with paragangliomas/pheochromocytomas.

Competency 2: Organ System Pathology; Topic EN: Endocrine. Learning Goal 5: Endocrine Neoplasms.

Part 1: Clinical Case

Patient Presentation

A 47-year-old male with no previous medical history presents to his family physician complaining of episodic headaches, sweating, heart palpitations, and a tremor. The symptoms started a few years ago, have become more frequent, and can last anywhere between a few seconds to an hour. The episodes often occur when the patient feels stressed or exercises. He is frustrated because nothing he does changes the severity of his symptoms. He does not have a history of serious illnesses, hospitalizations, or trauma. He is not on any medications. He has a family history of hypertension. He does not use tobacco products, cocaine, methamphetamines, or any other illicit drugs. He has not had fevers, chills, chest pain, shortness of breath, nausea, vomiting, or diarrhea.

On physical examination, vital signs showed an elevated blood pressure of 168/96 mm Hg, tachycardia of 116 beats per minute, a respiratory rate of 20 breaths per minute, and a temperature of 98°F (36.66°C). Physical examination reveals a diaphoretic male with no cardiopulmonary abnormalities other than the previously mentioned tachycardia.

Questions/Discussion Points, Part 1

What Is the Differential Diagnosis Based on the History and Physical Examination?

The differential diagnoses of episodic headaches, sweating, heart palpitations, and a tremor include pheochromocytoma, paraganglioma, essential hypertension, anxiety disorders, panic attack, thyrotoxicosis, medications, amphetamine and cocaine abuse, paroxysmal supraventricular tachycardia, and carcinoid syndrome. Neuroendocrine tumors secreting insulin (insulinoma)

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Table 1. Signs and Symptoms of a Pheochromocytoma.[1]

1. Sustained or paroxysmal hypertension
2. Tachycardia
3. Palpitations
4. Headache
5. Sweating
6. Tremor
7. A sense of apprehension

and heart failure are other considerations. A good medical history and imaging studies excludes several of these entities.

Part 2: Diagnostic Findings

Laboratory Studies

The complete blood count, comprehensive metabolic panel, D-dimer, and serial troponins were within reference ranges. An electrocardiogram indicated sinus tachycardia and left axis deviation consistent with left ventricular hypertrophy. A 24-hour urine fractionated metanephrine and catecholamine test showed significant elevations. Urinary metanephrines were 1300 μg/24 hours (normal range: 45-290 μg/24 hours).

Imaging

A chest X-ray was performed demonstrating mild left ventricular hypertrophy. Cardiac ultrasound demonstrated ventricular hypertrophy. No other abnormalities were present. An abdominal computed tomography (CT) scan showed a 3-cm-diameter left adrenal gland mass. The right adrenal gland was unremarkable.

Questions/Discussion Points, Part 2

What Entities Are in the Differential Diagnosis Based on the Above Laboratory Findings?

Elevated metanephrines and catecholamines are characteristic of a pheochromocytoma or paraganglioma.[1] Anxiety and panic disorders are also in the differential. Medications, for example, tricyclic antidepressants, are another consideration. Metanephrines may also be elevated in neuroblastoma, ganglioneuroblastoma, and ganglioneuroma. Measurement of urinary homovanillic acid and vanillylmandelic acid is the preferred screening laboratory test for these 3 entities.

Based on the Imaging Findings, What Entities Are in the Differential Diagnosis of an Adrenal Mass?

Pheochromocytoma, especially with elevated metanephrines, is the main consideration. Adrenal adenoma, adrenal carcinoma, myelolipoma, cyst, lipoma, metastatic cancer, hyperplasia, or tuberculosis can present as an adrenal mass.[2] Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma also present as adrenal masses. Paraganglioma would be an extra-adrenal mass.

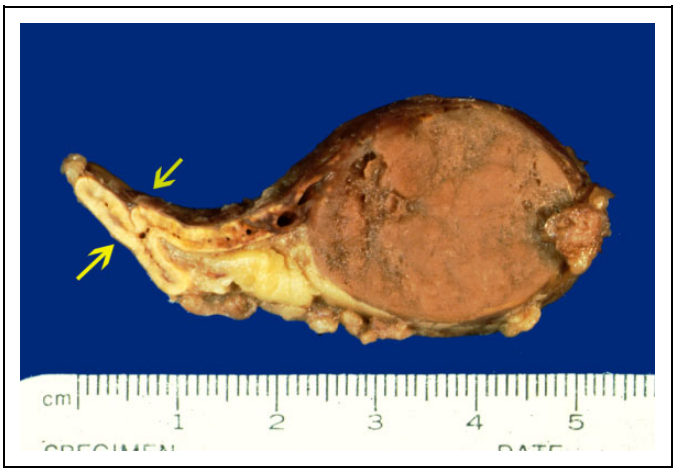

Figure 1. The adrenal gland is replaced with a central 3-cm-diameter brown tumor. A small portion of residual adrenal gland is present (arrows).

What Is the Diagnosis Based on the Clinical Scenario?

The paroxysmal headaches, sweating, heart palpitations, and hypertension (Table 1) with an abnormal 24-hour urine fractionated metanephrine and catecholamine test are consistent with a pheochromocytoma. This diagnosis is supported by an adrenal mass. The triad of headache, sweating, and heart palpitations should raise suspicion of a pheochromocytoma, especially when concurrent hypertension exists, but the triad is seen in less than 25% of patients with pheochromocytomas.[1-4]

Part 3: Diagnostic Findings

What Would Be the Next Step to Confirm the Diagnosis?

An adrenalectomy is indicated. Examination of the surgically removed adrenal gland showed a central brown tumor mass that originated in the adrenal medulla (Figure 1). Microscopic examination showed cells with abundant granular cytoplasm arranged in small nests surrounded by a thin fibrovascular stroma (Figure 2). Immunohistochemistry for the neuroendocrine markers, chromogranin and synaptophysin in the chief cells and S100 in the sustentacular cells were positive, supporting the diagnosis of a pheochromocytoma.

Questions/Discussion Points, Part 3

The gross and histological appearance of the tumor confirms the diagnosis. The term "pheochromocytoma" comes from the "dusky color" (dark brown) the tumor develops when immersed in a potassium dichromate solution.[1,4] Pheochromocytomas vary in appearance from well-circumscribed lesions to large hemorrhagic masses weighing up to 4 kg. On average, most pheochromocytomas weigh approximately 100 g.[1,2,4]

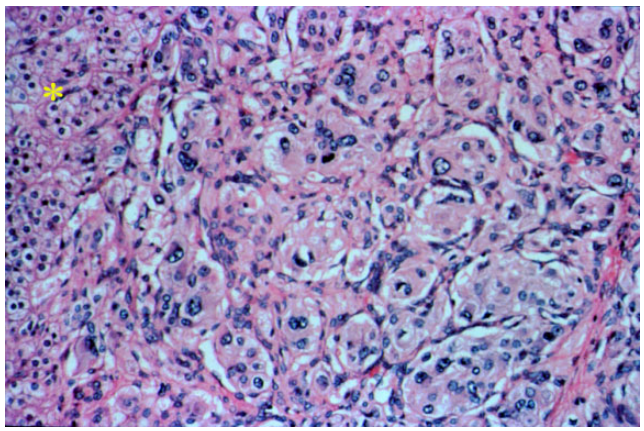

Figure 2. Polyhedral tumor cells with eosinophilic granular cytoplasm and ovoid nuclei are arranged in a characteristic alveolar "zellballen" or nesting pattern surrounded by thin fibrovascular septa. Residual adrenal cortex is present at the periphery (*). H&E, intermediate magnification.

Histology is variable in pheochromocytomas. The nesting, alveolar (zellballen) pattern is one of the more common patterns observed in pheochromocytomas. Polygonal to spindle-shaped chief cells surrounded by sustentacular cells give rise to the nesting pattern (Figure 2). Round to oval nuclei with a stippled chromatin pattern, commonly referred to as a salt and pepper pattern, is characteristic of neuroendocrine tumors including pheochromocytomas. Other histologic patterns observed on light microscopy include a diffuse, spindle, or small cell pattern, or a trabecular arrangement or sclerotic pattern. Immunohistochemistry and electron microscopy demonstrating membrane-bound secretory granules are helpful when the histologic pattern is equivocal.[1-4]

Malignant behavior absent metastatic disease is difficult to predict.[1-3] Pheochromocytomas with bland histology have metastasized to lymph nodes, liver, and lung.[2] In contrast, pheochromocytomas with marked pleomorphism have not been associated with metastases. As a generality, larger tumors with significant necrosis have a greater chance of being malignant. Histology in combination with the following factors (cellularity, necrosis, capsular or vascular invasion, type of catecholamine secreted, and MIB-1 immunoreactivity) is proposed to classify tumors from well differentiated to poorly differentiated with a 10-year survival based on degree of differentiation.[2]

What Is a Pheochromocytoma? How Does It Differ From a Paraganglioma?

Pheochromocytomas and paragangliomas are uncommon neuroendocrine tumors. A pheochromocytoma is a catecholamine-secreting tumor that develops from chromaffin cells in the adrenal medulla. The annual incidence is between 0.4 and 9.5 per 100 000 population. More recent data indicate that 1.5% to 18% of adrenal incidentalomas discovered during abdominal imaging for various reasons represent pheochromocytomas.[4,5] Most pheochromocytomas are sporadic and solitary tumors. Bilateral tumors are frequently observed in familial (hereditary) syndromes. Sporadic pheochromocytomas predominantly occur in adults, with the highest number in patients between 40 and 50 years of age.[4] Ten percent occur in children. Tumors associated with familial syndromes occur at an earlier age. The male:female ratio is equal.[4] Pheochromocytomas secrete both norepinephrine and epinephrine and present with the clinical findings in Table 1. Complications are listed in Table 2. Malignant potential is addressed above.[1-3]

Table 2. Possible Complications of a Pheochromocytoma.[1]

1. Catecholamine cardiomyopathy
2. Congestive heart failure
3. Pulmonary edema
4. Myocardial infarction
5. Ventricular fibrillation
6. Cerebrovascular accidents

The autonomic nervous system is divided into parasympathetic and sympathetic branches. Aggregates of autonomic neuronal cell bodies, referred to as ganglia, represent the cell bodies of postsynaptic neurons. Chromaffin cell tumors that have an extra-adrenal location arising from the sympathetic and parasympathetic ganglia (paraganglia) are called paragangliomas. Parasympathetic ganglia are mainly localized in the head and neck region. The carotid body tumor is an example of a parasympathetic paraganglioma. It is more frequent at high altitudes. Other sites include the vagus nerve, middle ear, and larynx.[2,3,6] Sympathetic ganglia are located along the vertebral bodies in the abdomen, pelvis, and thorax and sympathetic chain. Sites of involvement for sympathetic paragangliomas include the aortic bifurcation (Organ of Zuckerkandl), urinary bladder, heart, gallbladder, uterus, and adjacent to the spinal cord.[2,3,6] Paragangliomas possess the potential to secrete the catecholamine norepinephrine. Most paragangliomas in the head and neck region are nonfunctional with symptoms based on location. Malignant potential is approximately 5% for carotid body tumors and treatment is surgical resection. Germline mutations, as part of the hereditary paraganglioma syndrome, involving the succinate dehydrogenase gene, are observed.[2,3,6,7]

What Are the Possible Complications of a Pheochromocytoma?

Complications are often due to the sudden release of catecholamines (Table 2). Sudden release can cause congestive heart failure, pulmonary edema, myocardial infarction, ventricular fibrillation, and cerebrovascular accidents. It can also lead to catecholamine cardiomyopathy.[1] Malignant behavior with metastases is another complication.

Table 3. Hereditary Cancers Associated With Pheochromocytoma and Paragangliomas.[1-4,6,7]

Gene	Chromosome	Syndrome	Associated Features
RET	10q11.21	Multiple endocrine neoplasia 2A	Pheochromocytoma Medullary thyroid carcinoma Parathyroid hyperplasia
RET	10q11.21	Multiple endocrine neoplasia 2B	Pheochromocytoma Medullary thyroid carcinoma Marfanoid habitus Mucocutaneous ganglioneuromas
NF1	17q11.2	Neurofibromatosis, type 1	Pheochromocytoma Neurofibromatosis Café-au-lait spots Optic nerve glioma
VHL	3p25.3	Von Hippel-Lindau	Pheochromocytoma, paraganglioma
SDHA	5p15.33	Familial paraganglioma type 5	Pheochromocytoma, paraganglioma
SDHB	1p36.13	Familial paraganglioma type 4	Pheochromocytoma, paraganglioma
SDHC	1q23.3	Familial paraganglioma type 3	Pheochromocytoma, paraganglioma
SDHD	11q23.1	Familial paraganglioma type 1	Pheochromocytoma, paraganglioma
SDHAF2	11q12.2	Familial paraganglioma type 2	Pheochromocytoma, paraganglioma

What Different Hereditary Syndromes Are Associated With Pheochromocytoma and Paragangliomas?

Thirty percent of pheochromocytomas are familial with autosomal dominant inheritance and are associated with genetic mutations (Table 3).[1,7] Hereditary pheochromocytomas and paragangliomas occur in younger individuals, 15 to 20 years younger than those with sporadic tumors.[6] The mean age for pheochromocytomas in these individuals is 26 years (range: 12-48 years) and 29 years (range: 5-59 years) for paragangliomas.[3,4,6] Genetic mutations are classified into 2 groups, mutations involving the kinase signaling pathway (*RET* and *NF1*) and those with increased activity of the hypoxia-induced factor 1 (HIF-1α) transcription factor (*VHL*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, and *SDHAF2*).[1,7]

Von Hippel-Lindau syndrome is associated with a mutation in the *VHL* tumor suppressor gene. Clinically, Von Hippel-Lindau syndrome is characterized by headache, dizziness, weakness, visual deficits, and hypertension with a disease frequency of 1 in 30 000 to 40 000.[3] Symptoms are related to the underlying pheochromocytoma and hemangioblastomas in the brain and spinal cord and angiomas involving the retina and genitourinary tract. Cysts are frequent in the kidney and pancreas. There is also an increased incidence of renal cell carcinoma and neuroendocrine tumors. The *VHL* gene encodes for a protein downregulating HIF-1α leading to overexpression of vascular endothelial growth and other growth factors.[3,7]

Multiple endocrine neoplasia type 2 (MEN 2) syndrome with a prevalence of 1/40 000 individuals is associated with a mutation in the *RET* proto-oncogene that encodes for a receptor tyrosine kinase for glial-derived neurotropic factor. RET is present in urogenital and neural crest precursor cells as well as in the sympathetic, parasympathetic, and enteric nervous system. Multiple intracellular pathways involved in cell growth and differentiation are activated due to *RET* germline mutations.[7] Clinical features related to the underlying neoplasms include thyroid nodules and adenopathy secondary to medullary carcinoma and diarrhea secondary to high calcitonin levels. Symptoms secondary to parathyroid-related hypercalcemia or catecholamine release from a pheochromocytoma are less common.

Neurofibromatosis type 1 syndrome has an approximate frequency of 1 in 3000 and is associated with a *NF1* gene mutation that codes for the protein neurofibromin.[3,7] Neurofibromin acts as a negative regulator of RAS signaling. Loss of neurofibromin function leads to excessive RAS signaling. Clinical features include café au lait skin lesions, cutaneous and visceral neurofibromas, Lisch nodules, optic gliomas, and osseous lesions. Malignant nerve sheath tumors are also observed.[3,7]

Succinate dehydrogenase is a mitochondrial enzyme. Structurally, it is composed of 4 subunits: SDHA, SDHB, SDHC, and SDHD. Mutations involving these subunits affecting HIF-1α transcription factor lead to hereditary paraganglioma syndrome, a syndrome characterized by multiple paragangliomas and pheochromocytomas with a frequency of 1/300 000 (Table 3).[3,6,7] Familial paraganglioma variants, types 1, 3, and 4 are associated with mutations in *SDHD, SDHC*, and *SDHB* genes, respectively. Familial paraganglioma type 5 is associated with mutation in *SDHA* and familial paraganglioma type 2 with mutation in *SDHAF2* gene. Clinical features for patients with paragangliomas are based on the presence of a slow growing mass, tumor location (impingement on a critical structure), and whether the tumor is hormonally active. In contrast to pheochromocytomas that are frequently hormonally active, paragangliomas are less hormonally active. Many patients are asymptomatic with the lesion discovered during imaging workup for an abdominal condition or at autopsy.[4]

Each of the above hereditary syndromes, involving mutations in the succinate dehydrogenase gene, must be considered when evaluating a patient with a pheochromocytoma and/or paraganglioma.[1-4,6-12] Patients presenting at an early age with these neoplasms should be screened for mutations involving the succinate dehydrogenase gene.

Immunohistochemistry for SDHB has been used to screen for succinate dehydrogenase mutations.[2]

What Is the Rule of 10s?

Historically, the rule of 10s was applied to pheochromocytomas. The 10% rule outlined that 10% of pheochromocytomas (paragangliomas) were extra-adrenal, 10% of pheochromocytomas were bilateral, 10% were malignant, 10% were not associated with hypertension, and 10% occurred in children.[1] The 10% rule is called into question because tumor location (adrenal vs extra-adrenal) and likelihood of malignancy vary based on genetic mutations. Genetic involvement in tumors is closer to 30%. Fifty percent of familial pheochromocytomas are bilateral. Twenty to forty percent of paragangliomas are malignant and malignancy is more common in chromaffin tumors associated with germline mutations.[1-4,6,7]

Teaching Points

- A pheochromocytoma should be considered when evaluating an adrenal mass.
- The triad of headache, sweating, and heart palpitations should raise suspicion of a pheochromocytoma, especially when concurrent hypertension exists.
- Diagnosis of a pheochromocytoma is based on pathologic findings and is supported by an abnormal 24-hour urine fractionated metanephrine and catecholamine test.
- Pheochromocytomas are catecholamine-secreting tumors that originate in the adrenal medulla.
- Pheochromocytoma complications from catecholamine secretion include congestive heart failure, pulmonary edema, myocardial infarction, ventricular fibrillation, cerebrovascular accidents, and catecholamine cardiomyopathy.
- Paragangliomas are catecholamine-secreting tumors that arise from the autonomic nervous system ganglia that represent the cell bodies of postsynaptic neurons. Paragangliomas affect both the sympathetic and parasympathetic chains of the autonomic nervous system.
- Sign and symptoms associated with paragangliomas are based on tumor location, rate of growth, and whether they are hormonally active.
- Thirty percent of pheochromocytomas are familial with autosomal dominant inheritance and are associated with genetic mutations. Genetic mutations are classified into 2 groups, mutations involving the kinase signaling pathway (*RET* and *NF1*) and those with increased activity of the HIF-1α transcription factor (*VHL*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, and *SDHAF2*).
- The diagnosis of a pheochromocytoma at a young age warrants clinical and genetic testing for MEN2 syndrome, Von Hippel-Lindau syndrome, neurofibromatosis 1, and familial paraganglioma–pheochromocytoma syndromes.
- Malignant behavior absent metastatic disease is difficult to predict in these neuroendocrine tumors. Histology in combination with the following factors (cellularity, necrosis, capsular or vascular invasion, type of catecholamine secreted, and MIB-1 immunoreactivity) is proposed to classify tumors from well differentiated to poorly differentiated.

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Educational Case: Iron Overload and Hemochromatosis

Michael J. Borowitz, MD, PhD[1] and Alison Moliterno, MD[1]

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, hematopathology, anemia, iron overload, hemochromatosis, genetic mechanisms, inheritance patterns

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Primary Pathology Learning Objective

Objective HRC1.3: Hepcidin Regulation, Iron Overload, and Anemia of Chronic Disease: Discuss the role of hepcidin as an iron regulator and describe how different types of alterations in the hepcidin pathway can produce anemia of chronic disease or iron overload.

Competency 2: Organ System Pathology; Topic HRC: Hematopathology - Red Cell Disorders; Learning Goal 1: Anemia.

Secondary Pathology Learning Objective

Objective GM1.2: Inheritance Patterns: Compare and contrast the inheritance patterns of different types of Mendelian disorders and give examples of each type of pattern.

Competency 1: Disease Mechanisms and Processes; Topic GM: Genetic Mechanisms; Learning Goal 1: Genetic Mechanisms of Developmental and Functional Abnormalities.

Patient Presentation

A 50-year-old Caucasian male presented for evaluation concerned that he may be at risk of developing hemochromatosis based on his family history. His father presented at age 60 with bronzed skin and diabetes; he was found to have iron overload and subsequently has been undergoing therapeutic phlebotomies. The patient's medical history is unremarkable with the exception of hypercholesterolemia, for

Table 1. Iron and Genetic Studies of the Patient and His Father.

Lab Test	Father—Age 60	Patient—Age 50	Normal Range
Serum iron	232	106	65-170 μg/dL
Transferrin	284	230	200-400 mg/dL
Total iron binding capacity	355	288	250-450 mg/dL
% saturation	65	37	20%-55%
Ferritin	1518	217	10-300 ng/mL
HFE genotype C282Y	Homozygous	Heterozygous	

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Table 2. Iron and Genetic Studies of the Father and the Brother of the Patient.

Lab Test	Father—Age 60	Brother—Age 46	Normal Range
Serum iron	232	176	65-170 μg/dL
Transferrin	284	230	200-400 mg/dL
Total iron binding capacity	355	266	250-450 mg/dL
% saturation	65	65	20%-55%
Ferritin	1518	611	10-300 ng/mL
HFE genotype C282Y	Homozygous	Homozygous	

which he takes a statin. You decide to do some diagnostic blood work. In addition, the patient has provided you with results of blood work from his father.

Diagnostic Findings, Part 1

Results of iron studies and *HFE* studies are presented in Table 1.

Questions/Discussion Points, Part 1

Interpret the Father's and the Patient's Iron Studies

The father has elevated serum iron associated with increased transferrin saturation and an elevated ferritin indicative of both increased iron absorption and iron storage. The son has normal iron studies.

Do the Patient's Iron Studies Support the Diagnosis of Hemochromatosis?

No. He does not have evidence of either increased absorption or increased iron stores. Additionally, he is only a carrier of the *HFE* mutation, making it highly unlikely that he has a genetic predisposition to iron overload.

Ferritin and Serum Iron Reflect Different Aspects of an Individual's Iron Metabolism. What Is the Major Difference in the Type of Information Obtained From Each of These?

Ferritin is a measure of long-term iron storage, while serum iron (and transferrin saturation) better reflect daily iron absorption. Interpretation of ferritin testing can be misleading with only a single measurement because it is an acute phase reactant.

Diagnostic Findings, Part 2

After obtaining the results above, the patient consults his brother and recommends that he also undergo testing. Results from his brother, again in comparison to those of his father, are shown in Table 2.

Questions/Discussion Points, Part 2

Does His Brother Have Iron Overload? Why Is His Brother's Ferritin So Much Lower Than His Father's?

Yes, he has evidence of iron overload. He is younger than his father was at the time of his iron studies, and the degree of iron overload is a function of time.

Should Other Siblings Be Tested? What Would Be the Best Approach for Further Molecular Testing? If You Had Had the Opportunity to Evaluate the Father at the First Sign of Potential Iron Overload, What Testing Would You Have Done on Him?

Taking the brother's and father's genotypes together (and assuming the brothers have the same father!), mother must be a carrier, and other children have a 50% chance of being homozygotes also. *HFE* C282Y homozygotes in general will have an increased risk of significant iron overload. However, because there are significant modifiers of iron absorption beyond the *HFE* gene (age, gender, diet, and polymorphisms in other genes affecting iron absorption), not all homozygotes will have iron overload.[1] In this family, however, homozygotes do appear to have an increased risk of iron overload, so they should be identified. Because we know the mutation in this case, targeted mutation analysis for *HFE* C282Y is the only analysis needed.

If you had seen the father early in his course and had had no family history of hemochromatosis, it would be appropriate to do targeted analysis for both the *HFE* C282Y and H63D mutations, and if these were negative, sequence analysis could be used to identify other less common mutant alleles associated with *HFE*.

Which Genes Can Cause Hemochromatosis When Mutated? Describe the Inheritance Patterns Seen

The *HFE* C282Y on chromosome 6p22.2, as present in this case, is the most common mutation seen in classic (type 1 or *HFE*1) hemochromatosis and is associated with autosomal recessive inheritance. This mutation accounts for >80% of hemochromatosis cases.[2,3] Another common mutation in *HFE* (H63D) may be seen as a compound heterozygous (C282Y/H63D) genotype in some patients with hemochromatosis; patients with homozygous H63D rarely have clinically significant iron overload.[2,3] Four additional iron overload disorders labeled hemochromatosis have been identified[2]:

Juvenile hemochromatosis is the term given to clinically similar autosomal recessive diseases caused by mutations in 2 different genes:

*HFE*2A: the hemojuvelin (HJV) gene on chromosome 1q21.

*HFE*2B: the hepcidin (HAMP) gene on chromosome 19q13.

*HFE*3, also autosomal recessive, is caused by a mutation in transferrin receptor 2 gene on chromosome 7q22.
*HFE*4, is autosomal dominant and caused by a mutation in SLC40A1 gene on chromosome 2q32.

Discuss the Pathophysiology of How Iron Overload Occurs in Hemochromatosis

Patients with hemochromatosis have in common low hepcidin levels. Hepcidin normally binds ferroportin in both duodenal enterocytes and reticuloendothelial macrophages, which in turn blocks release of iron from these cells. Thus, hepcidin serves to keep iron from being absorbed from the gut or being released from storage macrophages back into circulation. In the absence of hepcidin, this process is reversed, with increased iron absorption and increased turnover of iron from reticuloendothelial macrophages leading to high levels of both serum ferritin and saturation of transferrin and ultimately to iron deposition in tissues.[3]

Teaching Points

- Iron overload can be suspected from serum iron studies, in particular elevated serum iron and transferrin, and increased transferrin saturation.
- In the absence of a historical explanation for iron overload (such as multiple blood transfusions), patients with iron overload should be investigated for genetic disorders, and in particular for hereditary hemochromatosis.
- If hereditary hemochromatosis is identified, family members should be tested for evidence of iron overload as well.
- Other factors modify the effects of the abnormal gene so that affected family members may vary significantly in their clinical and laboratory presentations.
- The most common form of hereditary hemochromatosis is called type 1 and is due to a mutation in the *HFE* gene. It is inherited as an autosomal recessive.

Declaration of Conflicting Interests

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Educational Case: Thyroid Neoplasms: Pathogenesis, Diagnosis, and Treatment

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, endocrine, follicular adenoma, follicular carcinoma, papillary thyroid carcinoma, thyroid neoplasms

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Primary Objectives

Objective EN5.1: Thyroid Neoplasms. Compare and contrast the clinicopathologic features of follicular adenomas, follicular carcinoma, and papillary thyroid carcinoma.

Competency 2: Organ System Pathology; Topic EN: Endocrine; Learning Goal 5: Endocrine Neoplasms.

Patient Presentation, 1

A 30-year-old female presents with a palpable right thyroid nodule. The nodule was first noticed 3 months ago and has increased in size slightly over time. The patient denies having hoarseness, dysphagia, weight changes, intolerance to cold or hot weather, drowsiness, or palpitations. A serum thyroid-stimulating hormone (TSH) test was performed, and it was within normal limits. Ultrasonography (US) of the thyroid revealed a solitary well-circumscribed nodule on the right lower lobe of the thyroid measuring 2.0 × 1.5 × 1.0 cm.

Diagnostic Findings, Part 1

What Is Your Differential Diagnosis Based on the Clinical History?

Palpable thyroid nodules can be found in 5% of women and 1% of men.[1] The prevalence can increase to 20% to 70% if nonpalpable nodules are included, and these are usually detected by ultrasound or autopsy.[2] Around 7% to 15% of all nodules are thyroid cancers[1]; therefore, thyroid nodules should be evaluated accordingly. The differential diagnosis for a thyroid solitary nodule with a normal TSH in decreasing order of frequency is hyperplastic nodule, follicular adenoma, papillary thyroid carcinoma (PTC), and follicular carcinoma. Other neoplasms are much less frequent.

Questions/Discussion Points, Part 1

What Testing Is Available for This Patient and Which Is Recommended?

As per the 2015 American Thyroid Association Management Guidelines, nodules greater than 1 cm should be further evaluated.[1] Serum TSH levels can be measured. If the TSH of the patient is low, a radionuclide (preferably ^{123}I) thyroid scan should be performed to document whether the

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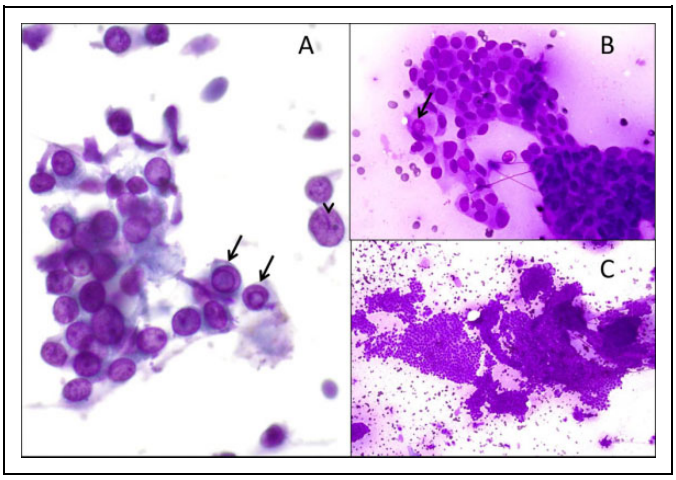

Figure 1. A and B, Cytology of thyroid fine needle aspiration (FNA) showing papillary thyroid carcinoma (PTC) nuclear changes: grooves (arrowhead), intranuclear pseudoinclusions (arrow), nucleoli, and powdery chromatin, as well as nuclear crowding and nuclear enlargement (A, PAP stained, high-power 60× magnification, B, Diff quick-stained intermediate power 40× magnification). C, A papillary formation is observed. (diff quick stained, low power 10× magnification).

nodule is hyperfunctioning ("hot"), isofunctioning ("warm"), or nonfunctioning ("cold").[1] Hyperfunctioning nodules rarely harbor malignancy.[1]

Thyroid US is considered the imaging modality of choice for the investigation of thyroid nodules. Several features are assessed with the US, including number, size, margin, contours and shape of the nodule, cystic or solid nodule, vascularity, and presence of calcifications, among others. Individual US features may have limited value distinguishing between benign and malignant thyroid nodules, but when multiple signs of malignancy appear in combination, it is possible to make an accurate prediction. Some of the US features suggestive of malignancy are ill-defined nodule, irregular margins, hypervascularity, microcalcifications or coarse calcifications, solid and hypoechoic nodule, and invasion of surrounding tissue.[3]

A fine needle aspiration (FNA) biopsy will be the procedure of choice in the evaluation of a thyroid nodule larger than 1 cm.[1] Nodules smaller than 1 cm are not usually biopsied unless they have sonographically suspicious features or other risk factors for malignancy, such as history of thyroid cancer and radiation exposure, among others.[2] Fine needle aspiration is the most cost-effective and least invasive procedure that will help guide the management and treatment of a patient. Fine needle aspiration can be performed either with palpation or under ultrasound guidance, depending on the location of the nodule or how difficult it is to palpate or properly fix the target.

Diagnostic Findings, Part 2

The patient underwent an US-guided thyroid FNA biopsy. Microscopic examination of the smears stained by Papanicolaou method showed clusters and papillary fragments of follicular cells with nuclear enlargement, pale nuclei, powdery chromatin, nuclear pseudoinclusions, and nuclear grooves (Figure 1).

Based on the Cytological Findings, What Is the Correct Diagnosis?

The smears showed the classic cytologic features of a PTC, malignant (Bethesda VI). Since the risk of malignancy for this lesion is 94% to 99%, a near total thyroidectomy or lobectomy is indicated for this patient.

What Is the Bethesda System and How This Can Aid in the Management and Treatment of the Patient?

The Bethesda System for Reporting Thyroid Cytology (BSRTC) is a set of recommendations on how to report thyroid cytology specimens in diagnostic categories with associated risk of malignancy and patient management (Table 1[4]). It is a consensus on terminology and morphologic criteria that aims to facilitate communication among the different disciplines in clinical medicine and pathology.

Using the BSRTC, a diagnosis of malignancy (PTC) on FNA is made whenever the cytomorphologic features are conclusive for malignancy. The criteria for reporting PTC are follicular cells arranged in papillae (fibrovascular cores) or syncytial monolayers with the characteristic nuclear features such as enlarged oval or irregular nuclei, nuclear crowding, longitudinal nuclear grooves, intranuclear cytoplasmic pseudoinclusions, pale nuclei with powdery chromatin, and psammoma bodies (not always present).

Questions/Discussion Points, Part 2

What Are the Clinical Presentation and Biologic Behavior of PTC?

Papillary thyroid carcinoma usually presents as a solitary, painless nodule, and around 30% of patients might also have associated lymphadenopathy.[5] It tends to grow very slowly and usually involves only 1 thyroid lobe. In large tumors, the presentation will include dysphagia, stridor, and cough.[5] In some cases, these neoplasms are discovered incidentally during the workup of a different problem.[5]

Papillary thyroid carcinoma is the most common thyroid cancer and accounts for approximately 80% of malignant neoplasms of the thyroid with a female to male ratio of 4:1.[2,5] It is associated with radiation exposure and its incidence is higher in areas with high iodine intake.[5]

Describe the Pathological Features of PTC

The gross pathology is variable from well-circumscribed nodule to diffuse involvement of the lobe, or multifocal.[5] The cut surface is white-gray, firm, and granular with possible presence of calcifications.[5] The microscopic histologic features are similar to the

Table 1. The Bethesda System for Reporting Thyroid Cytology Diagnostic Categories.[4]

Diagnostic Category		Risk of Malignancy (%)	Management
I	Nondiagnostic or Unsatisfactory	5-10	Repeat FNA with ultrasound guidance
II	Benign	0-3	Clinical and sonographic follow-up
III	Atypia of uncertain significance or Follicular lesion of uncertain significance	~10-30	Repeat FNA, molecular testing, or lobectomy
IV	Follicular neoplasm or Suspicious for a follicular neoplasm	25-40	Molecular testing, lobectomy
V	Suspicious for malignancy	50-75	Near total thyroidectomy or lobectomy
VI	Malignant	97-99	Near total thyroidectomy or lobectomy

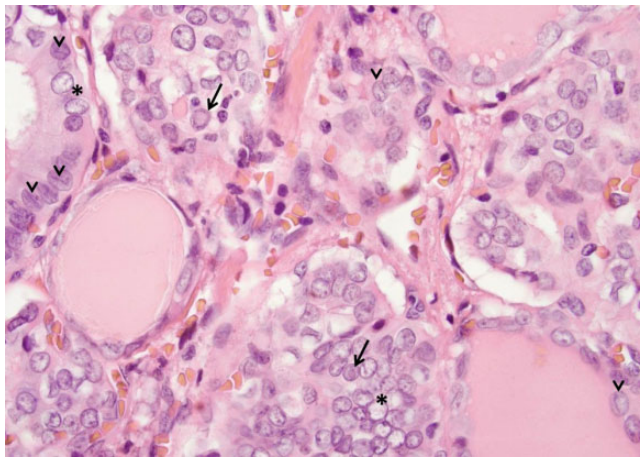

Figure 2. Histology of papillary thyroid carcinoma (PTC) showing nuclear changes: chromatin clearing known as "Orphan Annie eye" nuclei (asterisk), grooves (arrow head), intranuclear pseudoinclusions (arrow), nucleoli, powdery chromatin, crowding, and overlapping (H&E stained, high power 60× magnification).

cytologic features. The papillary structures are more evident and contain complex branching true papillae with fibrovascular cores.[5] The neoplastic cells will show the classic chromatin clearing called "Orphan Annie eye" nuclei (Figure 2A).[5] There are different variants of PTC (classic or usual, microcarcinoma, follicular variant, diffuse sclerosing variant, cribriform-morular variant, oncocytic variant, tall cell variant, columnar cell variant) and their microscopic characteristics will vary slightly from the classic PTC; however, they must present the characteristic nuclear features (Figure 2B).[5] The classic or usual variant is the most common presentation of PTC, representing ~75% to 80% of cases.

What Genetic Mutations Does This Neoplasm Harbor?

Papillary thyroid cancers frequently have genetic mutations and rearrangements that lead to activation of the mitogen-activated protein kinase that promotes cell division.[6] In PTC, the most commonly identified mutations in this pathway are point mutations of the *BRAF* and *RAS* genes and *RET/PTC* rearrangement, found in >70% of cases.[6] The most common genetic alteration is the *BRAF* point mutation (V600E), identified in ~45% of PTC cases.

Genetic alterations involving the tyrosine kinase signaling pathways (*RET/RAS/RAF* pathway) are interconnected with the epidermal growth factor receptor activation cascade, which leads to the syntheses of vascular endothelial growth factor (VEGF) and VEGF receptor, which has also been found in PTC, particularly in tumors with *BRAF* mutations. Drugs targeting these pathways could play a significant role in controlling the progression of the disease.

How Is Molecular Testing Useful in Management of Thyroid Nodules?

Approximately 10% to 15% of thyroid nodules on FNA fall into the indeterminate category which includes follicular and oncocytic neoplasms (Bethesda IV) and atypia of undetermined significance/follicular lesion of undetermined significance (Bethesda III), according to the most current categorization.[4] For these cases, molecular testing is recommended for management since thyroid cancers are commonly associated with specific molecular alterations.

What Are the Treatment Options for Thyroid Cancer?

Treatment options for thyroid cancer include surgery, radioactive iodine (^{131}I) ablation (RAI), molecular-targeted therapies with several tyrosine kinase inhibitors, and external beam radiation. Surgery is the treatment of choice; however, the extent of the surgery is still controversial (total thyroidectomy vs near total thyroidectomy vs. lobectomy).[5] Lymph node sampling can be performed if there is clinical or radiographic enlargement. The most common complications after surgery are damage to the recurrent laryngeal nerve and hypoparathyroidism. The postoperative disease status can be evaluated with postoperative serum thyroglobulin and/or ultrasound.[1]

Radioactive iodine is used in coordination with thyroidectomy to completely ablate the thyroid gland and to eradicate possible residual cancer. The first-dose administration is referred to as ablation, whereas subsequent administrations for residual disease is referred to as treatment.[3]

Tyrosine kinase inhibitors, which primarily target angiogenesis (specifically VEGF receptor signaling pathways), are used to treat patients with recurrent or metastatic thyroid cancers who do not respond to RAI and TSH-suppressive

hormone therapy.[3,7] Two drugs, Sorafenib and Lenvatinib, are approved by the Food and Drug Administration for use in selected patients with refractory metastatic differentiated thyroid cancers.

External beam radiation therapy is only used for palliative treatment of patients with advanced or inoperable thyroid cancer and it may be administered in the adjuvant setting, after surgical resection, or as primary treatment. It is usually considered in patients over 45 years of age who have grossly visible extrathyroidal extension and a high likelihood of residual disease during surgery, and it is also reserved for tumors that are unresponsive to RAI.[3]

What Is the Prognosis of Patients With PTC?

In general, PTC is indolent and has an excellent prognosis.[2,5] The 10-year survival rate is greater than 90%.[2] Although the prognosis is excellent, certain clinical and pathologic features have been identified that portend a somewhat higher risk of tumor recurrence and cancer-related mortality, including over 45 years of age, male gender, size of carcinoma being greater than 2 cm^3, invasion into surrounding tissue, histological subtype, and distant metastasis. It spreads mostly by lymphatic channels and metastasis to lymph nodes is frequent; however, this does not affect prognosis.[5]

The histological subtypes of PTC associated with worse prognosis are tall cell, insular, and hobnail variants. Patients with aggressive histologic subtypes are usually treated more aggressively.[8] In addition to its strong correlation with PTC, the *BRAF* V600E mutation has also been associated with poor prognosis and higher recurrence rate.

Patient Presentation, 2

A 55-year-old woman presents with a painless, slowly enlarging left thyroid mass. A previous FNA of the lesion was reported as suspicious for a follicular neoplasm (Bethesda IV). Following this diagnosis, the patient underwent a total thyroidectomy.

Diagnostic Findings, Patient 2

On gross examination, there is a solitary encapsulated mass, measuring 3 cm in greatest dimension. Microscopically, the tumor is surrounded with a capsule (encapsulated) and shows a microfollicular pattern. Upon thorough examination of the capsule, an area where the tumor cells penetrate through the whole thickness of the capsule was found. This is referred as capsular invasion; therefore, a diagnosis of follicular carcinoma was reported.

Questions/Discussion Points, Patient 2

What Are the Cytologic and Pathologic Features of Follicular Carcinoma?

The cytomorphology on FNA specimens will show a marked cellularity, consisting predominantly of small clusters of

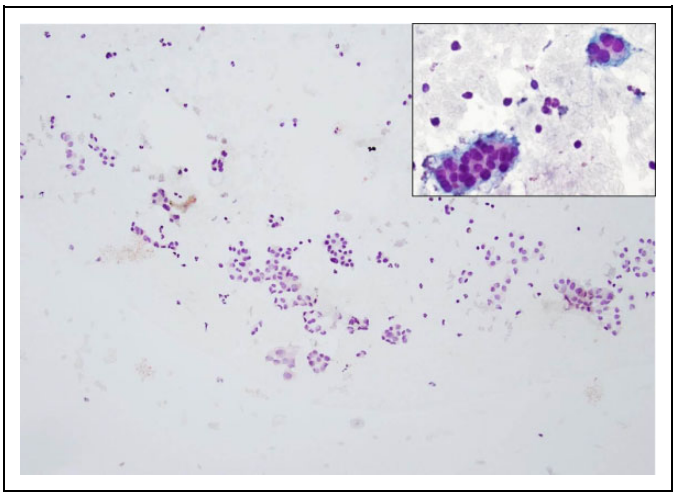

Figure 3. Cytology of thyroid fine needle aspiration (FNA) showing microfollicles of a follicular neoplasm (PAP stained, low power 10 × magnification). Papillary formations as seen here are composed of follicular cells surrounding a fibrovascular core.

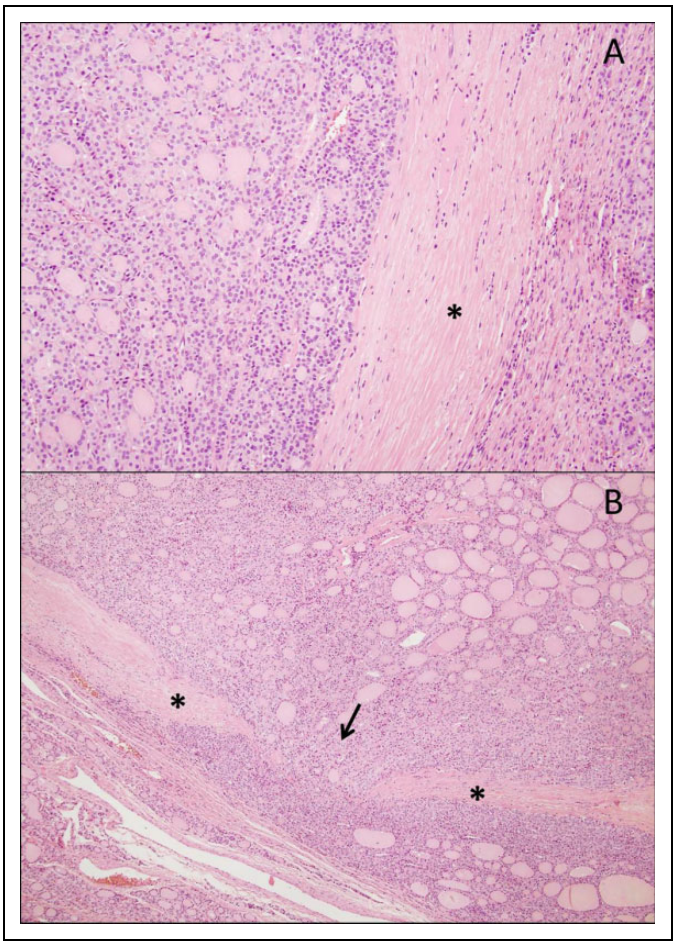

Figure 4. A, Histology of follicular adenoma showing a fibrous capsule (asterisk) and a microfollicular pattern on left side of image (H&E stained, intermediate power 40× magnification). B, Evident capsular invasion (arrow) is present in follicular carcinoma. Capsule is shown with asterisks (H&E stained, intermediate power 40× magnification).

follicular cells called microfollicles, with scant colloid in the background (Figure 3). The cytology of adenoma and carcinoma can be almost identical, so they are both diagnosed as suspicious for a follicular neoplasm (Bethesda IV).

The distinction between the 2 is made by examining the capsule for invasion after resection. The resection specimen of follicular adenoma and carcinoma will show a fibrous capsule grossly and a microfollicular pattern microscopically (Figure 4A).[5] These lesions will lack the characteristic nuclear features of PTC.[5] To differentiate a follicular adenoma from a carcinoma, evident capsular invasion must be present (Figure 4B). This distinction is only diagnosed on the resected specimen, and thorough examination of the capsule is required. In follicular carcinomas, the most common alterations include *RAS* mutations and *PAX8-PPARγ* rearrangement.[6] Many of these mutations are being explored as therapeutic targets for thyroid cancer.[6]

Follicular adenomas are treated with lobectomy and have an excellent long-term prognosis.[5] The treatment of choice for follicular carcinoma is surgery (lobectomy or thyroidectomy). A lobectomy is more likely to be performed in younger patients (<45 years), with a single nodule (<40 mm), and without thyroiditis or metastatic disease.[5] Radioactive iodine therapy can be indicated in patients with lymph node metastasis who underwent total thyroidectomy. Follicular carcinoma has an excellent long-term prognosis on minimally invasive lesions, 97% 20-year survival and a 50% 20-year survival on widely invasive lesions.[5]

Teaching Points

- Thyroid nodules are a common finding, and only 7% to 15% are malignant.
- Papillary thyroid carcinoma is the most common thyroid malignancy and presents with characteristic nuclear features on microscopic examination.
- The BSRTC is a guideline to create uniformity in reporting thyroid lesions on FNA.
- Most common mutation of PTCs is the point mutations of the *BRAF* gene.
- To differentiate a follicular adenoma from a follicular carcinoma, a thorough examination of the capsule should be done to assess capsular invasion.

Declaration of Conflicting Interests

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Educational Case: Chronic Lymphocytic Leukemia

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, chronic lymphocytic leukemia, classification, hematopathology, morphology

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Primary Objective

Objective HWC3.1: Morphology of Acute Leukemia and Lymphoma. Describe the morphologic features that characterize typical cases of acute leukemia and lymphoma.

Competency 2: Organ System Pathology; Topic HWC: Hematopathology—White Cell Disorders, Lymph Nodes, Spleen, and Thymus; Learning Goal 3: Classification of Leukemia and Lymphomas.

Patient Presentation

A 65-year-old man pursued laboratory testing as part of health screening offered by his employer and was advised to visit his physician based on initial test results. He has not experienced any acute symptoms (fever, chills), nor weight loss, but does report feeling more tired the past few months. The patient did not have any personal or family history of cancer and is not currently taking any medications. Physical examination is unremarkable. There is no organomegaly or palpable lymphadenopathy on physical examination.

Diagnostic Findings

Complete blood count (CBC) is provided in Table 1. The automated differential count is provided in Table 2.

Questions/Discussion Points

What Is the Differential Diagnosis Based on Review of the Complete Blood Count Values? What Would Be the Next Step in the Diagnostic Evaluation?

Review of the CBC values reveals an elevated white blood cell (WBC) count (leukocytosis). The automated differential count provided by the automated hematology analyzer shows a predominance of lymphocytes among the white cells (lymphocytosis). The differential diagnosis for lymphocytosis is quite broad and would include chronic lymphoid neoplasms as well as reactive causes such as viral infections, hepatitis, pertussis (whooping cough), autoimmune disease, and polyclonal B lymphocytosis (usually in middle-aged women with a smoking history). The clinical history does not provide an obvious reactive explanation for the lymphocytosis, and therefore

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Table 1. Complete Blood Count.

Test	Patient	Normal Range
WBC	14 K/μL	4.8-10.8 K/μL
Hemoglobin	13.6 g/dL	13-16.8 g/dL
Hematocrit	41%	40%-50%
MCV	91 fL	80-100 fL
Platelets	400 K/cu mm	150-450 K/cu mm

Abbreviation: WBC, white blood cell; MCV, mean corpuscular volume.

Table 2. Automated Differential Count.

Differential Count	Patient Percentage	Patient Absolute ($\times 10^3/\mu L$)	Normal Range Absolute ($\times 10^3/\mu L$)
Granulocytes	20	2.8	1.4-6.5
Lymphocytes	75	10.5	1.2-3.4
Monocytes	5	0.7	0.1-0.6
Eosinophils	0	0	0-0.5
Basophils	0	0	0-0.2

chronic lymphoid neoplasms should be strongly considered. Examples of chronic lymphoid leukemias or lymphomas which may present with leukocytosis would include chronic lymphocytic leukemia, T-cell large granular lymphocytic leukemia, hairy cell leukemia variant, prolymphocytic leukemia, adult T cell leukemia/lymphoma, Sezary syndrome, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, and mantle cell lymphoma.

An important next step would be to review the peripheral smear. Given that an automated WBC differential analysis may occasionally misclassify blasts, lymphocytes, and atypical lymphocytes, and the fact that some artifacts (platelet clumps, nucleated red blood cells [RBCs], incomplete lysis of RBCs, etc) may result in a falsely elevated WBC, review of the peripheral blood smear enables the confirmation of cell counts, as well as the assessment of the morphology of the abnormal population.[1]

How Does Review of the Peripheral Blood Film Help Refine This Differential Diagnosis?

An image from the patient's peripheral blood film is shown in Figure 1A. Review confirms the predominance of small, monotonous-appearing lymphocytes which show smooth nuclear contours and mature morphology. Maturity can be determined by assessing the nuclear features: in the current case, the lymphocytes show clumped chromatin (Figure 1A), in contrast to the finely dispersed, open chromatin that characterize immature blast cells of an acute leukemia (Figure 1B). The monotonous appearance and lack of morphologic heterogeneity of the small lymphocytes is another clue that the proliferation is neoplastic. In both examples, "smudge" cells, which represent disrupted lymphocytes, are present due to the lymphocytosis and fragility of the lymphocytes.

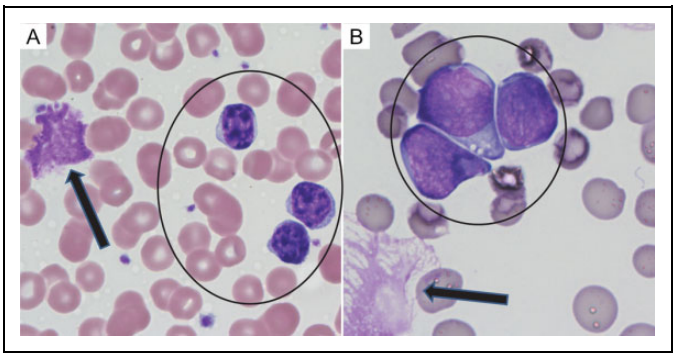

Figure 1. A, Chronic lymphocytic leukemia (CLL). Note the mature, clumped chromatin and smooth nuclear contours of the CLL cells (circle) and smudge cells in the background (arrows). B, Acute lymphoblastic leukemia (ALL). Note the finely dispersed chromatin in the leukemic blast cells (circle). Note that smudge cells are not specific for CLL and can also be seen in ALL (arrow).

What Diagnostic Study Would Be Most Helpful to Confirm Your Suspicions? What Result Would You Expect to See?

In order to confirm the morphologic suspicion of a chronic lymphoid neoplasm, flow cytometry would be the preferred ancillary study and could be performed on the peripheral blood sample. In this technique, the cells are incubated with fluorescently tagged antibodies specific for hematolymphoid markers and are subsequently interrogated by a laser beam in a single cell suspension. If the marker is present, the fluorescent signal is detected, enabling the rapid characterization of the antigen profile of cells. In this particular case, the neoplastic cells were positive for the CD19, CD20 (dim), CD5, and CD23, with monotypic expression of lambda immunoglobulin light chain (Figure 2). The expression of CD19 and CD20 would indicate B cell lineage, and the monotypic surface light chain expression can be used as a surrogate for clonality and aid in the establishment of a neoplastic B lymphoid process. The dim level of expression of CD20 and surface light chain, together with the coexpression of CD5 and CD23, are characteristic for chronic lymphocytic leukemia (CLL), which is the most common adult leukemia in the Western world.[2] By definition, there must be $\geq 5 \times 10^9$ monoclonal B CLL cells/L in the peripheral blood in order to distinguish CLL from monoclonal B lymphocytosis (MBL). This distinction is important because MBL is not considered a frank malignancy, and only a small fraction of MBL patients will develop overt CLL. When the same cells infiltrate soft tissues or lymph nodes, a diagnosis of small lymphocytic lymphoma (SLL) is rendered (Figure 3). Chronic lymphocytic leukemia and SLL are now considered to be different clinical manifestations of the same disease.

What Organ Systems Are Involved in This Disorder? How Would You Stage This Patient?

CLL/SLL may involve many organ systems, although many patients with CLL are asymptomatic when initially diagnosed.

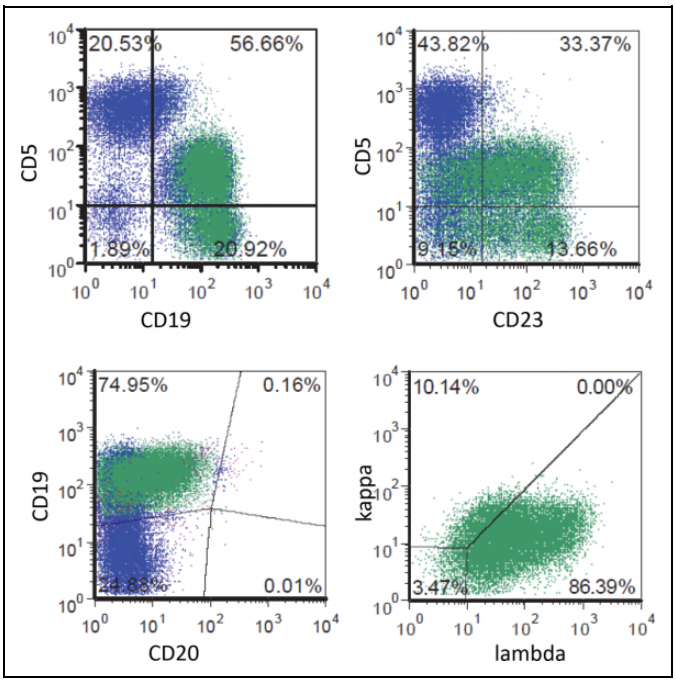

Figure 2. Flow cytometric phenotype of chronic lymphocytic leukemia (CLL). The neoplastic B cells (green) are positive for CD19, CD5, CD23, CD20 (dim intensity), and show restricted lambda immunoglobulin light chain expression.

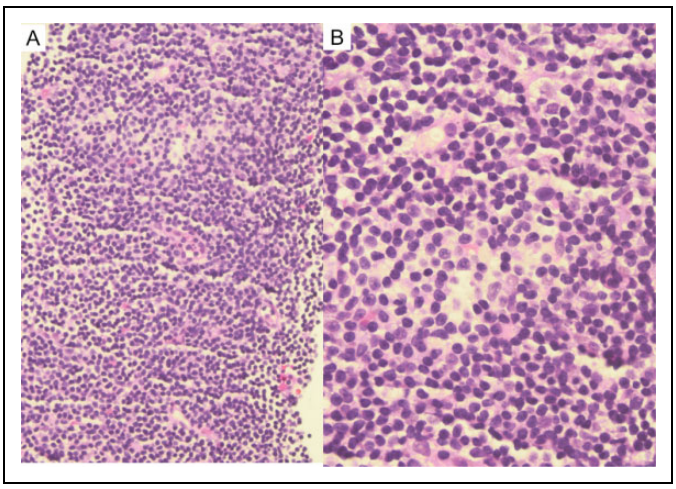

Figure 3. Small lymphocytic lymphoma (SLL). A, The lymph node architecture is replaced by a proliferation of small, relatively monotonous-appearing lymphoid cells. B, Higher magnification shows round nuclear contours and mature, clumped chromatin.

Patients with SLL present with lymphadenopathy, hepatosplenomegaly, or other symptoms of organ infiltration and disruption. In about 10% to 15% of cases, CLL/SLL may also be associated with autoantibodies, resulting in an immune-mediated hemolytic anemia or thrombocytopenia. CLL/SLL may be associated with neutropenia and hypogammaglobulinemia, which leads to an increased susceptibility to infections.[2]

Table 3. Rai Staging of Chronic Lymphocytic Leukemia.

Rai Stage	Findings
0	Asymptomatic lymphocytosis
I	Lymphocytosis and lymphadenopathy
II	Lymphocytosis, lymphadenopathy, organomegaly*
III	Lymphocytosis and anemia, with or without lymphadenopathy and/or organomegaly
IV	Lymphocytosis and thrombocytopenia, with or without lymphadenopathy, organomegaly, and/or anemia

*Organomegaly = hepatomegaly and/or splenomegaly.

Table 4. Binet Staging of Chronic Lymphocytic Leukemia.

Binet Stage	Findings
A	No anemia or thrombocytopenia and <3 involved areas*
B	No anemia or thrombocytopenia and ≥3 involved areas
C	Anemia and/or thrombocytopenia, and any number of involved areas

*Areas considered are head and neck including the Waldeyer ring (counts as 1 area), axilla, groin/superficial femoral, palpable spleen, and palpable liver.

The Rai and Binet staging systems have traditionally been used to stage patients with CLL/SLL. These staging systems take into account the degree of the cytopenias and the presence or absence of lymphadenopathy or organomegaly on physical examination (Tables 3 and 4).[3] This patient would be best staged as Rai stage 0 or Binet stage A due to asymptomatic lymphocytosis without anemia, thrombocytopenia, or any lymphadenopathy or organomegaly on physical examination. In patients with asymptomatic, early-stage CLL, routine surveillance with computed tomography (CT) scans is not recommended, as these studies do not improve survival and expose the patients unnecessarily to small doses of radiation.[4]

What Testing Could Be Performed to Help Predict the Clinical Course? What Would Be Your Treatment Recommendations?

Useful markers for risk stratification have included assessing for specific genetic abnormalities, which can be performed on the diagnostic peripheral blood sample. Prognostic markers that may be helpful include fluorescence in situ hybridization (FISH) studies to evaluate for deletion (del) 11q, del 17p, trisomy 12, and del 13q, and assessment of the mutation status of the *TP53* and immunoglobulin heavy chain (*IGHV*) genes.[5] In this particular patient, FISH studies only showed an isolated del 13q abnormality, and molecular studies revealed a mutated *IGVH* gene status. There was no evidence of unfavorable prognostic markers such as del 11q, del 17p or *TP53* mutations, or an unmutated *IGHV* gene status.

The clinical behavior of CLL/SLL is variable, and early treatment of asymptomatic patients does not result in improved survival.[3] Therefore, given the overall favorable prognostic profile and lack of symptoms in this patient, observation (or "watchful waiting") may be the best course of action. Indications for treatment include progressive cytopenias, bulky or symptomatic lymphadenopathy or splenomegaly, B symptoms, or other signs or symptoms of disease progression. In a minority of cases (5%-10%), there is transformation to a more aggressive lymphoma ("Richter syndrome"), most commonly diffuse large B cell lymphoma, often presenting as a rapidly enlarging mass.[2]

Current therapies for CLL/SLL emphasize a multimodality approach including monoclonal antibodies targeting the B cell marker CD20 (such as rituximab), combined with chemotherapeutic agents such as purine analogs (fludarabine) or alkylating agents (cyclophosphamide, bendamustine). Agents targeting B cell receptor signaling (ibrutinib, idelalisib) or expression of the anti-apoptotic protein BCL2 (venetoclax) are also increasingly being incorporated into therapeutic regimens for CLL/SLL.[5]

Teaching Points

- Chronic lymphocytic leukemia is the most common adult leukemia in the Western world and may be asymptomatic at diagnosis
- Chronic lymphocytic leukemia is characterized by an absolute lymphocytosis composed of monomorphic, small, mature-appearing lymphoid cells
- Flow cytometry can be used to assess the immunophenotype of leukemic cells and demonstrate the characteristic phenotype
- The clinical behavior is heterogeneous, with many patients not requiring initial therapeutic intervention

Declaration of Conflicting Interests

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Educational Case: Endocrine Neoplasm: Medullary Thyroid Carcinoma

Sheila Segura, MD[1], Gloria Ramos-Rivera, MD[1], and Mark Suhrland, MD[1]

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Abstract

Medullary thyroid cancer is a rare neuroendocrine tumor that arises the neural crest-derived parafollicular C cells and accounts for approximately 5% to 10% of thyroid cancers worldwide. These tumor can occur sporadically or as part of hereditary tumor syndromes, such as multiple endocrine neoplasia 2 and familial medullary thyroid cancer. The most common clinical presentation is a solitary thyroid nodule. The genetic defect in these disorders involves the RET proto-oncogene which is important for diagnosis of medullary thyroid cancer (including screening for hereditary medullary thyroid cancer) and for treatment guidance. This review summarizes the molecular basis and clinicopathologic features of medullary thyroid carcinoma.

Keywords

pathology competencies, organ system pathology, endocrine neoplasms, medullary thyroid carcinoma, cytologic diagnosis, molecular basis, clinical features, pathologic features

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Primary Objective

Objective EN5.2: Medullary Thyroid Carcinoma: Describe the molecular basis and clinicopathologic features of medullary thyroid carcinoma.

Competency 2: Organ System Pathology; Topic Endocrine (EN); Learning Goal 5: Endocrine Neoplasms.

Patient Presentation

A 45-year-old woman presented to her endocrinologist with a single, gradually increasing nodule in her right neck. There was no relevant past medical or family history. She also mentioned having diarrhea intermittently. During her initial visit, the patient was in good condition, her blood pressure was 110/70 mm Hg, and her pulse was 75/minute and regular. Physical examination revealed a 2.0-cm firm mass with smooth borders on the right side of the thyroid that moved with swallowing. The rest of the examination was unremarkable. Ultrasonography of the thyroid revealed a 2.2-cm solid right thyroid nodule. The results of thyroid function tests were normal Thyroid-stimulating hormone (TSH) = 0.6 μIU/mL [range: 0.5-4.70 μIU/mL], T4 = 5.5 μg/dL [4.5-12.5 μg/dL], T3 = 115 ng/dL [80-200 ng/dL], and free T4 = 1.0 ng/dL

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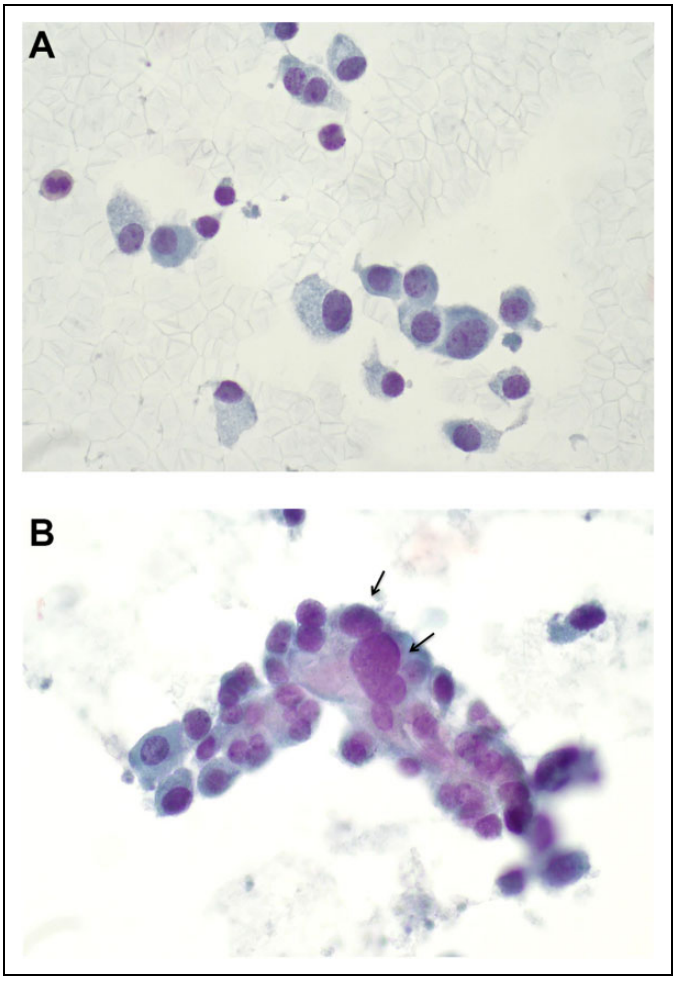

Figure 1. A, Smears show singly dispersed plasmacytoid (eccentric nuclei) cells of variable sizes, abundant amphophilic cytoplasm, granular chromatin, and inconspicuous nucleoli (PAP-stained, high power ×60 magnification). B, Smear shows a loosely cohesive cluster of neoplastic cells with occasional nuclear enlargement (arrows; PAP-stained, high power ×60 magnification).

[0.8-1.8 ng/dL]). However, the preoperative serum calcitonin value of 150 pg/mL (normal values: <8.8 pg/mL for men, <5.8 pg/mL for women; by immunochemiluminometric assay) and her serum calcium of 25 mg/dL (range: 8.5-10.5 mg/dL) were elevated. Fine-needle aspiration (FNA) biopsy of the nodule was performed.

Diagnostic Cytologic Findings

Microscopic examination of the FNA smears stained by Papanicolaou method showed loosely cohesive clusters and single plasmacytoid cells of variable sizes. The cells had eccentric nuclei with granular chromatin ("salt and pepper") and abundant cytoplasm (Figure 1A and B). Occasional cells with nuclear enlargement were also seen (Figure 1). Immunohistochemical stains performed on the cellblock showed that the neoplastic cells were positive for calcitonin (Figure 2) and negative for thyroglobulin.

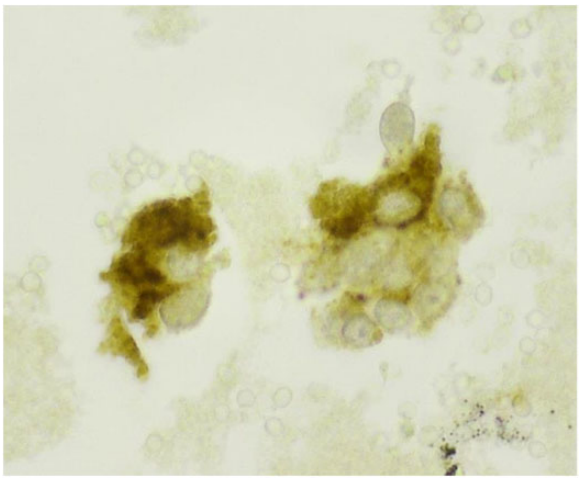

Figure 2. Immunohistochemical stain, performed on the cellblock, shows that the neoplastic cells are positive for calcitonin (cytoplasmic and granular staining; high power ×60 magnification).

Questions/Discussion Points

What Is Your Differential Diagnosis Based on the Clinical History and Cytologic Findings?

The differential diagnosis includes metastatic neuroendocrine carcinoma, poorly differentiated thyroid carcinoma (insular carcinoma), lymphoma, and medullary thyroid carcinoma. Based on the cytological features and immunohistochemical profile, a diagnosis of medullary thyroid carcinoma was rendered.

The patient was referred to a thyroid surgeon, and total thyroidectomy with cervical lymph node dissection was carried out. The tumor was 2.3 cm in greatest dimension with focal capsular invasion without any lymph node involvement. Pathologic findings in the thyroid gland were consistent with medullary thyroid carcinoma (Figure 3).

What is Medullary Thyroid Carcinoma?

Medullary thyroid cancer (MTC) is a rare neuroendocrine tumor that arises from C cells (formerly called parafollicular cells) which are derived from the neural crest. Medullary thyroid cancer accounts for approximately 5% to 10% of thyroid cancers worldwide, and approximately 1% to 2% of thyroid cancer in United States.[1] The C cells are located throughout the thyroid gland, but they are predominant at the junction of the upper third and lower two-thirds of each lobe, which is where the majority of MTCs are found. C cells secrete a variety of peptides and hormones, and MTC is characterized by the secretion of calcitonin, which is used as a diagnostic and prognostic marker in MTC.[2]

How Does Medullary Thyroid Cancer Manifest?

Most medullary thyroid carcinomas are sporadic. However, approximately 20% to 25% of cases are familial and are usually

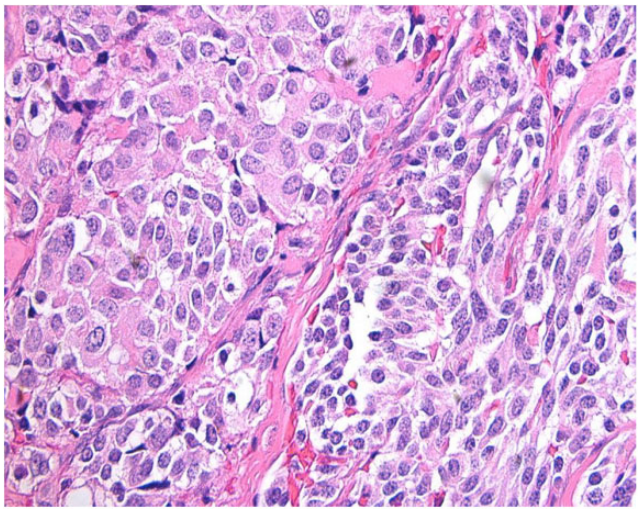

Figure 3. Section of the thyroid nodule showing nests of round and spindle cells outlined by fibrous tissue. The cells display granular cytoplasm and round nuclei with "salt and pepper" chromatin. (Hematoxylin and eosin stained slide, high power ×40 magnification).

a component of multiple endocrine neoplasia (MEN) syndrome 2A or 2B or present as pure familial MTC (FMTC) syndrome.[3]

Sporadic Medullary Thyroid Cancer

Sporadic MTC accounts for approximately 75% to 80% of all cases of medullary thyroid cancer. There are typically unilateral with no associated endocrinopathies. The typical age of presentation is in the fourth and sixth decades of life, more commonly affecting women in a 3:2 ratio. The most common clinical presentation of sporadic MTC is that of a solitary thyroid nodule (35%-50%) or enlarged lymph node (up to 70%).

The tumors are generally unilateral and tend to arise in the posterior thyroid. In some patients, MTC presents with symptoms suggesting invasion of the surrounding structures (dysphagia, hoarseness, and/or respiratory difficulty) or can present with distant metastases at the time of diagnosis. The most common locations for metastatic MTC are the mediastinum, liver, lungs, and bone.[1-3]

Systemic symptoms may occur due to hormonal secretion by the tumor. Tumor secretion of calcitonin, calcitonin gene-related peptide, or other substances (calcitonin, prostaglandins, serotonin, or vasoactive intestinal polypeptide) can cause diarrhea or facial flushing in patients with advanced disease.[1,3]

Hereditary (Familial) Medullary Thyroid Cancer

Multiple Endocrine Neoplasia 2A (Sipple Syndrome)

Multiple endocrine neoplasia 2A syndrome or Sipple syndrome is the most common form of MEN 2 syndrome, accounting for 75% of hereditary MTC. It is associated with MTC, pheochromocytoma (~50%), and hyperparathyroidism (~20%). This syndrome is inherited in an autosomal dominant manner, affecting males and females equally. Peak incidence of syndromic MTC is in the 30s, ranging from adolescence to early adulthood.[3,4]

Multiple Endocrine Neoplasia 2B

Multiple endocrine neoplasia 2B accounts for 8% to 15% of all patients with MEN 2. It is associated with MTC and pheochromocytoma, and an unusual physical appearance, characterized by mucosal ganglioneuromas and marfanoid habitus (long limbs, hyperlaxity, and arachnodactyly). Inheritance is autosomal dominant as in MEN 2A, again equally affecting males and females.[3] Patients with MEN 2B present MTC early in life, diagnosed in infancy or early childhood before their 30s.[3] Almost 100% of patients with MEN 2B develop MTC with the disease having a more aggressive course.

Familial Medullary Carcinoma Without Associated Endocrinopathies

The FMTC category of MTC is the least aggressive and is defined as MTC without other hereditary endocrine tumors. Similar to other types of thyroid cancers, the peak incidence is between the ages of 40 and 50 years.[3]

What Are the Genetic Features of Medullary Thyroid Cancer?

The genetic defect in these disorders involves the RET proto-oncogene on chromosome 10q11.2. RET is a single-pass transmembrane receptor belonging to the tyrosine kinase superfamily. The germ line RET mutations lead to the activation of major intracellular pro-oncogenic pathways (eg, RAS/MAPK, JUN kinase, PI3K/AKT, and nuclear factor-κB), that is central for the development of sporadic and hereditary MTC. Currently known RET mutations account for about 95% of MEN 2A and 85% of FMTC families. Somatic RET point mutations have been identified in about 50% of patients with sporadic MTC.[1-4]

Mutations involving the RET proto-oncogene are also seen in other malignant and nonmalignant diseases. Chromosomal translocations activating RET proto-oncogene can occur in 20% to 30% of patients with papillary thyroid carcinoma, and can also be seen, but less frequently, in patients with lung adenocarcinoma and chronic myelomonocytic leukemia. Inactivating RET mutations occur in patients with hereditary and sporadic Hirschsprung disease (HD).[5]

Describe the Pathological Features of Medullary Thyroid Cancer

Grossly, sporadic or hereditary MTC present as a well-demarcated, solid, white-gray/yellow, firm, and gritty

nodule of variable size. Sporadic MTC tumors typically present as a single and unilateral nodule. Hereditary MTC are usually bilateral, multicentric, single, or multiple nodules. Although the tumors in sporadic and hereditary MTC are sharply circumscribed, they are not encapsulated. Medullary thyroid cancer typically is the first neoplasm observed in both MEN 2A and MEN 2B syndromes. Both sporadic and FMTC arise at the junctions of the upper and middle thirds of the lateral lobes.[3]

The histopathology is quite variable and numerous histological subtypes are described. The characteristic features of MTC, in both sporadic and familial, are sheets, nests, or trabecular arrangement of cells which can vary in shape, round, polygonal, spindle, or giant cells, all with varying amount of granular cytoplasm. Tumor cells usually have uniform, round to oval nuclei with granular or punctate chromatin, also referred to as "salt and pepper" chromatin. Fibrous or amyloid stroma can be present. The hereditary MTC is usually preceded by "C-cell hyperplasia" (CCH) and usually occurs in the upper two-thirds of the thyroid adjacent to a MTC or may be seen in asymptomatic carriers of RET mutation. Multiple CCH foci are a hallmark of MEN 2 syndromes and FMTC syndrome. The presence of neoplastic CCH foci is considered a paradigm of a genetically determined condition.[1-4]

How Is Medullary Thyroid Cancer Diagnosed?

Fine needle aspiration cytology is a widely utilized tool for the diagnosis of thyroid lesions with a high degree of sensitivity, specificity, and diagnostic accuracy. It is a simple, rapid, and cost-effective test that can effectively distinguish between neoplastic and nonneoplastic lesions of the thyroid. Fine-needle aspiration can effectively triage patients with thyroid nodules as to who require surgery and who do not.[6,7]

In the year 2007, the National Cancer Institute (NCI), Bethesda, Maryland, organized the NCI Thyroid Fine Needle Aspiration State-of-the-Science Conference, and an initiative was undertaken to publish an atlas and guidelines using a standardized nomenclature for the interpretation of thyroid FNAs, known as the Bethesda system for reporting thyroid cytopathology. The atlas describes 6 diagnostic categories of lesions: Nondiagnostic/unsatisfactory, benign, atypical follicular lesion of undetermined significance, "suspicious" for follicular neoplasm, suspicious for malignancy, and malignant. The 6 diagnostic categories of the Bethesda system have individual implied risks of malignancy that influence management paradigms.[7]

The diagnosis of MTC is usually made after FNA biopsy. The patients typically present with high calcitonin serum levels that can also be helpful for diagnosis. Fine-needle aspiration smears of MTC nodules show variable cytologic features. The classic smear pattern is usually cellular, yielding tumor cells that are dispersed and are characterized by eccentric nuclei (plasmacytoid cell pattern), granular chromatin (neuroendocrine-type), and inconspicuous nucleoli in a relatively clean background. The cytoplasm of the tumor cells is faintly granular but may show conspicuous red granules. Deposition of amorphous, glassy, eosinophilic material consistent with amyloid, can be seen in the background, and sometimes is confused with colloid material.

Depending on the specific cytomorphology of the tumor, a number of differential diagnoses may arise and immunohistochemical staining may be helpful. The small cell pattern may be mistaken for a malignant lymphoma (CD45 positive), poorly differentiated thyroid carcinoma (thyroglobulin positive), or metastatic small-cell carcinoma (calcitonin negative) among others. When MTC is suspected on cytological examination, immunohistochemical staining for calcitonin is important for making a diagnosis of MTC.

The 2015 American Thyroid Association (ATA) guidelines for MTC management recommend that all cases of MTC, either sporadic or inherited, and patients with CCH, should be analyzed for germ line mutations in the RET proto-oncogene. RET molecular diagnosis is considered the gold standard for the recognition of patients at risk of MTC in MEN 2 families, and the recommended method of initial testing for patients with MEN 2 is either a single or a multitiered analysis to detect RET mutations in exon 10 (codons 609, 611, 618, and 620), exon 11 (codons 630 and 634), and exons 8, 13, 14, 15, and 16.[5]

The ATA also recommends that genetic counseling and genetic testing should be offered in patients with sporadic MTC found to have a RET mutation; in first-degree relatives of patients with proven hereditary MTC; in parents whose infants or young children have the classic phenotype of MEN 2B; in infants or young children with HD and RET germ line mutations, and in adults with MEN 2A who have symptoms suggestive of HD.[5]

Describe the Treatment Options for Medullary Thyroid Cancer

Standard treatment for MTC requires surgical removal of the thyroid with regional lymph node dissection. Unlike other thyroid malignancies, MTCs are resistant to radioactive iodine therapy because they do not concentrate radioactive iodine. The extent of the surgical resection and lymph node dissection is determined by the size of the primary tumor, the extent of nodal, and distant metastases. In the presence of advanced metastatic disease, a more palliative approach is recommended, and aggressive neck surgery is typically not performed to improve quality of life.

Prophylactic thyroidectomy is recommended in patients with germ line RET mutations, and the timing of surgery depends on the type of MEN syndrome and the RET mutation, but it is usually recommended before the onset of clinically significant disease.

For patients with metastatic MTC, treatment depends on the extent of metastases. Surgery may be an option for surgically resectable tumor lesion to relieve tumor burden. Conventional chemotherapy has limited efficacy in patients

with MTC. A new class of therapies targeting the RET receptor tyrosine kinase family has been developed because of its role in the pathogenesis of MTC. Several clinical trials have been developed involving tyrosine kinase inhibitors (such as sorafenib, sunitinib, vandetanib, motesanib, and cabozantinib) with the rationale that they can block the molecular pathways involved in MTC. Some of these treatments (like vandetanib and cabozantinib) have been approved by the US Food and Drug Administration for the treatment of adults with symptomatic or progressive metastatic MTC.[2,8]

What Are the Features That Drive Prognosis in Patients With Medullary Thyroid Cancer?

The size of the primary tumor and the presence of nodal and distant metastasis are important factors predicting survival in patients with MTC. When the tumor is localized to the thyroid gland, the 10-year survival rate is approximately 75% to 95%. Patients with regional lymph node disease have a 5-year overall survival rate of 75.5%. Distant metastases at initial diagnosis is associated with a poor prognosis, with a 10-year survival rate of <50%.[2,8] Younger age (<40 years old) at the time of diagnosis is associated with better prognosis.

Factors that may also predict a poor prognosis includes:

1. Calcitonin doubling times less than 6 to 12 months is associated with poor survival, while doubling times >24 months are associated with a very favorable prognosis.
2. Specific germ line mutations in RET predict the aggressiveness of the tumor (MEN 2B have worse *a* prognosis).

Recurrent disease develops in approximately 50% of patients with MTC. Calcitonin levels are very sensitive for detecting either residual or recurrent disease.

Teaching Points

- Medullary thyroid cancers are rare tumors that arise from the neural crest–derived parafollicular C cells.
- They occur sporadically or as part of hereditary tumor syndromes (MEN 2 and FMTC).
- A solitary thyroid nodule is the most common presentation of sporadic MTC (in 75%-95% of patients). In most patients, the disease involves regional lymph nodes at the time of diagnosis.
- Genetic testing for RET mutations is important for diagnosis of MTC (including screening for hereditary MTC) and for treatment guidance. Therefore, germ line RET testing is recommended in all patients with newly diagnosed CCH or apparently sporadic MTC.
- Due to limited adjuvant treatment options, adequate initial surgical management is essential to the successful treatment of MTC.
- New molecular targeted treatment options are available in cases of distant or recurrent disease not amenable to surgery.

Declaration of Conflicting Interests

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Educational Case: Head and Neck Neoplasia: Salivary Gland Tumors

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, head and neck neoplasia, salivary gland tumor, warthin tumor, pleomorphic adenoma, mucoepidermoid carcinoma

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Primary Pathology Learning Objective

Objective HN2.1. Benign and Mucoepidermoid Tumors of Salivary Glands. Distinguish the clinicopathologic features of the 2 benign tumors (pleomorphic adenoma or mixed tumor and Warthin tumor) from the malignant mucoepidermoid carcinoma.

Competency 2: Organ System Pathology, Topic: Head and Neck (HN), Learning Goal 2: Head and Neck Neoplasia

Secondary Pathology Learning Objective

Objective CYP1.2. Categorizing Diagnostic Certainty: Compare and contrast the degree of diagnostic certainty applied to general diagnostic categorization in cytologic diagnosis.

Competency 3: Diagnostic Medicine and Laboratory Diagnosis; Topic CYP: Cytopathology; Learning Goal I: Cytologic Diagnosis

Patient Presentation

A 62-year-old obese, hypertensive, Caucasian male presents to his primary care physician with a slowly growing left cheek mass for 1-year duration. He has a 40 pack-year smoking history. He has no family or personal history of carcinoma. He is HIV-negative and has not experienced any dysphagia, odynophagia, B-symptoms, trismus, or facial weakness.

Diagnostic Findings, Part 1

On physical examination, his primary care physician notes a palpable, 2 cm, "doughy," mobile mass in his left parotid gland. There appears to be mild erythema and slight puckering of the skin overlying the mass. The contralateral parotid gland has no palpable masses and there is no cervical lymphadenopathy. Tongue sensation and facial nerve function are intact. The patient undergoes imaging studies and fine needle aspiration (FNA) biopsy of his lesion.

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Questions and Discussion Points, Part 1

Given the Clinical History, What Are the Most Likely Salivary Gland Neoplasms This Patient Might Have, and What Clinical Features Would Suggest Each Diagnosis?

Salivary gland tumors are rare, making up less than 2% of all tumors. Up to 80% of salivary gland tumors appear in the parotid gland, and 70% of parotid gland tumors are benign. Parotid gland neoplasms are more likely to be benign than submandibular gland neoplasms, which are more likely to be benign than minor salivary gland neoplasms, which are more likely to be benign than sublingual gland neoplasms. Although certain clinical features can be suggestive, they are unreliable to definitively differentiate between benign or malignant.[1,2]

The most common salivary gland tumor is pleomorphic adenoma and makes up approximately 50% of all salivary gland tumors and 80% of all benign salivary gland tumors. They typically are painless, mobile, and slow growing and occur most frequently in the parotid gland—features all seen in our patient. However, pleomorphic adenoma occurs more frequently in females, and the average age of presentation is in the mid-40s—unlike our patient.[1-3]

Warthin tumor is the second most common salivary gland neoplasm and occurs almost exclusively in the parotid gland. It is seen more frequently in male patients, the average age of presentation is in the mid-60s, and it has a strong correlation with smoking history. In addition, the "doughy" texture of the mass is a frequent finding in Warthin tumor. Up to 10% of Warthin tumors are multifocal, and up to 15% of Warthin tumors occur bilaterally, so either of these features would also raise the suspicion for this diagnosis.[1,2] However, our patient's lack of a contralateral mass on physical examination certainly does not rule out this diagnosis.

Mucoepidermoid carcinoma is the most common malignant salivary gland neoplasm. It affects a broad age range and is the most common primary malignant salivary gland tumor in both adults and children. It is likely to demonstrate symptoms related to its invasive nature, including rapid growth, pain, immobility, skin changes and facial asymmetry, cervical lymphadenopathy, and loss of nerve function.[1,2] The patient demonstrated few of these concerning symptoms (mild erythema and slight puckering overlying the mass) and the diagnosis is lower on the differential.

In summary, the differential diagnosis includes but is certainly not limited to pleomorphic adenoma, Warthin tumor, and mucoepidermoid carcinoma. The skin erythema and puckering may be seen in a malignant process (mucoepidermoid carcinoma); however, the mobility, painlessness, slow growth, and absent lymphadenopathy suggest a benign tumor (Warthin tumor or pleomorphic adenoma). These features combined with the "doughy" texture, patient's smoking history, male sex, and patient age suggest a Warthin tumor.

What Risk Factors Predispose a Patient to Develop Salivary Gland Neoplasms?

Ionizing radiation, in the form of atomic bomb exposure, previous head and neck radiation therapy, and radioactive iodine treatment for thyroid disease, have all shown an increased association with the development of salivary gland neoplasms. There is also a strong association with smoking and the development of Warthin tumor—smokers are 8 times more likely to have a Warthin tumor than the general population. Certain genetic alterations occur more frequently in certain salivary gland tumors but familial aggregation has not yet been observed in salivary gland tumors.[1]

What Diagnostic Testing Is Available for This Patient?

Although the clinical history and certain physical examination findings, such as mobility of the mass or overlying skin changes, can suggest a benign or malignant process, computed tomography, magnetic resonance imaging (MRI), and ultrasonography are much more accurate. Imaging is primarily used to assess malignant features, rather than to ascertain a specific diagnosis. Imaging studies can determine if a neoplasm is contained within the salivary gland or if it has invaded into adjacent structures. It can also assess regional lymph node and distant metastases. However, a tissue biopsy is ultimately required to make a diagnosis in salivary gland tumors. Tissue biopsy can be performed via fine needle aspiration biopsy or core needle biopsy.[2]

What Are the Advantages and Limitations of Fine Needle Aspiration in Presurgical Assessment of Salivary Gland Tumors?

Salivary gland tumors are a heterogeneous and morphologically diverse group of benign and malignant neoplasms. They are often sampled by fine needle aspiration and/or core needle biopsy, but given the significant overlap in morphology and immunohistochemical staining between salivary gland tumors, tissue biopsy still has limitations in its ability to confer a definitive diagnosis. Accuracy of FNA diagnosis varies across studies and practitioners. Generally, cytologic sampling has approximately 96% to 98% sensitivity in identifying a salivary gland neoplasm, with 79% sensitivity and 96% specificity in distinguishing benign from malignant tumors. Even in the absence of a definitive diagnosis, however, tissue biopsy can still help narrow down the differential, making it a valuable tool in triaging patients for medical or surgical management. Core biopsy may offer better accuracy than FNA biopsy, but it also causes more discomfort to the patient and has greater risk of complications, such as nerve damage and tumor seeding along the needle tract.[4]

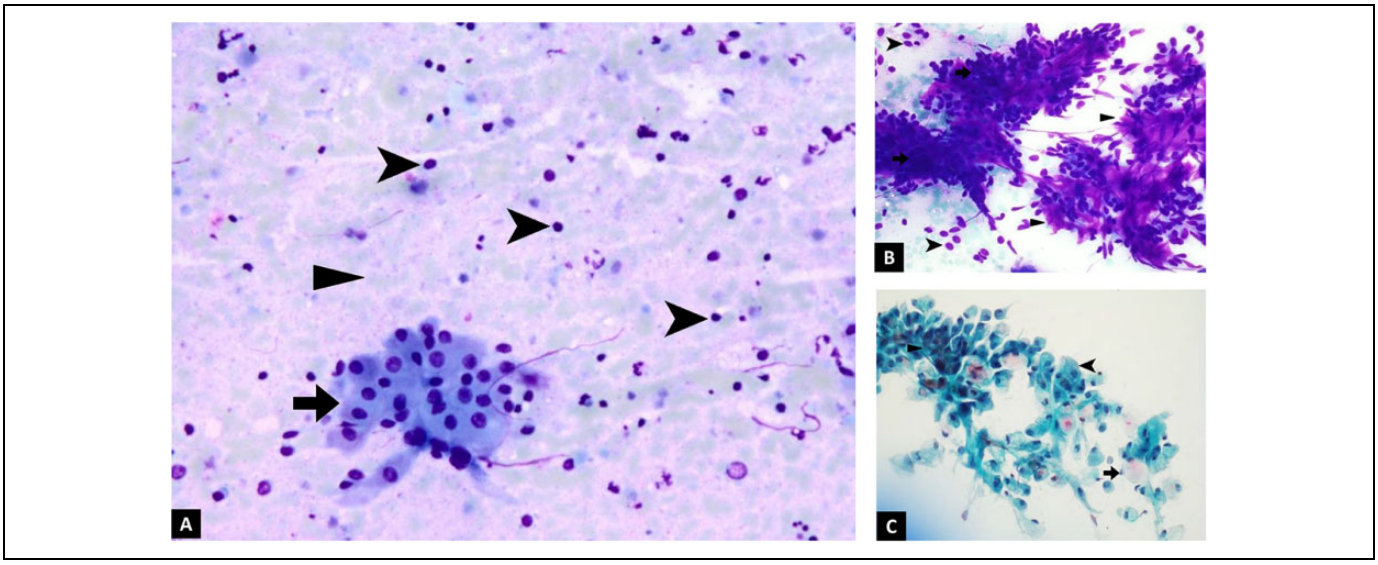

Figure 1. Cytologic features. A, FNA biopsy of the patient's lesion, showing Warthin tumor with sheets and clusters of oncocytic cells (arrow), lymphocytes (arrowhead), and granular debris in the background (triangle). B, Cytology of pleomorphic adenoma for comparison, with cohesive sheets and clusters of ductal cells (arrow), individual myoepithelial cells (arrowhead), and metachromatic, magenta-colored, fibrillary stroma (triangle). C, Cytology of mucoepidermoid carcinoma for comparison, with signet-ring type mucin producing cells (arrow), polygonal squamoid cells with dense blue cytoplasm (arrowhead), and smaller intermediate cells (triangle).

Diagnostic Findings, Part 2

Magnetic Resonance Imaging

The patient undergoes MRI of the neck with and without contrast, which demonstrates 2 enhancing parotid masses located in the superficial lobe of the left parotid gland. The masses measure 1.2 × 0.8 × 0.9 cm and 0.7 × 0.6 × 0.5 cm. The deep parotid lobes are not involved. The right parotid gland is unremarkable. No infiltrative features or cervical lymphadenopathy are seen.

Cytologic Assessment

Upon biopsy of the larger lesion, thick, green-brown fluid is aspirated, resembling motor oil. A representative photomicrograph of the FNA biopsy of the patient's larger lesion is shown in Figure 1A.

Questions and Discussion Points, Part 2

How Do the Findings on MRI Help Narrow Down the Differential?

Since no infiltrative features or cervical lymphadenopathy are seen, a benign neoplasm is favored. On imaging, the tumor was found to be 2 separate nodules, rather than a solitary lesion that was noted on physical examination. The clinical presentation plus the features seen on radiology (multiple lesions with no infiltrative features) make a diagnosis of Warthin tumor likely.

Discuss the Cytologic Features of the Fine Needle Aspirate Biopsy in Figure 1A

The "motor oil" fluid that is aspirated from the lesion is a common feature of Warthin tumor. The biopsy of the tumor has 3 distinct features, which are diagnostic of Warthin tumor: sheets and clusters of oncocytic cells (arrow), lymphocytes (arrowhead), and granular debris in the background (triangle).

The Cytologic Features of the 2 Other Neoplasms Considered in the Differential Diagnosis Are Shown in Figure 1B and C for Comparison. What Features Distinguish the Patient's Warthin Tumor From Pleomorphic Adenoma and Mucoepidermoid Carcinoma?

Figure 1B: Pleomorphic adenoma: This tumor has cohesive sheets and clusters of ductal cells (arrow), individual myoepithelial cells (arrowhead), and metachromatic, magenta-colored, fibrillary stroma (triangle) when stained with a modified Wright Giemsa (Diff Quik) stain.

Figure 1C: Mucoepidermoid carcinoma: This tumor has a mixed population of cells, with 3 distinct cell types. Signet-ring type mucin producing cells with pink mucin (arrow), polygonal squamoid cells with dense blue cytoplasm (arrowhead), and smaller intermediate cells (triangle) when stained with a Papanicolaou stain.

What Are the Treatment Options for the Patient?

Treatment recommendations are currently based on retrospective reviews and not randomized clinical trials. Complete surgical resection with negative margins is the gold standard, and patients with benign tumors (such as Warthin tumor and pleomorphic adenoma) and low-grade tumors can be treated by surgery alone. High-grade tumors, tumors with positive resection margins, and tumors with high-risk features are usually treated with surgery

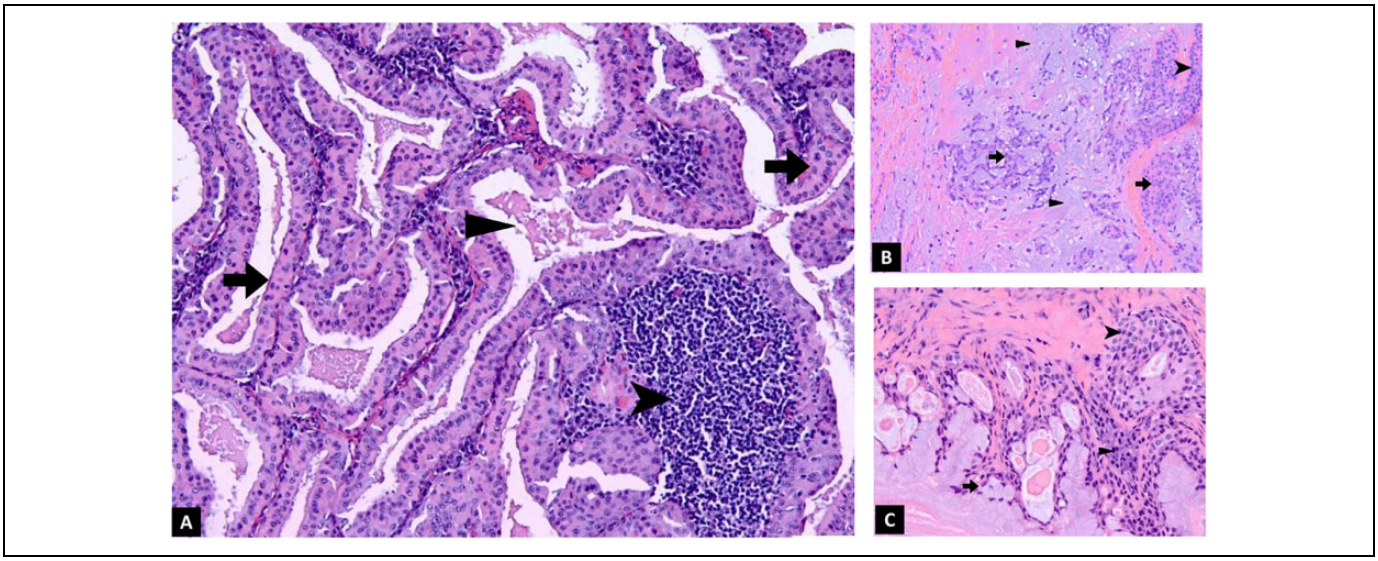

Figure 2. Histologic features. A, Surgical excision of the patient's lesion showing Warthin tumor with oncocytic cells (arrow) and lymphoid stroma (arrowhead). Granular debris fills the cyst spaces (triangle). B, Histology of pleomorphic adenoma for comparison, with ductal cells (arrow) surrounded by a layer of myoepithelial cells (arrowhead), arranged in a chondromyxoid stroma (triangle). C, Histology of mucoepidermoid carcinoma for comparison, with mucin producing cells (arrow), squamoid cells (arrowhead), and intermediate cells (triangle).

and adjuvant radiation therapy. Because he has a benign diagnosis of Warthin tumor, he can be treated with surgery alone.[5]

Diagnostic Findings, Part 3

Histologic Assessment

The patient undergoes superficial parotidectomy to remove the 2 masses. A representative photomicrograph of the patient's lesions is shown in Figure 2A.

Questions and Discussion Points, Part 3

Discuss the Histologic Features of the Surgical Excision in Figure 2A

The cystic lesion is lined by oncocytic cells (arrow) with a lymphoid stroma (arrowhead). Granular debris fills the cyst spaces (triangle). These are diagnostic of and consistent with the initial biopsy diagnosis of Warthin tumor.

The Histologic Features of the 2 Other Neoplasms Considered in the Differential Diagnosis Are Shown in Figure 2B and C for Comparison. What Features Distinguish the Patient's Warthin Tumor From Pleomorphic Adenoma and Mucoepidermoid Carcinoma?

Figure 2B: Pleomorphic adenoma: This tumor has ductal cells (arrow) surrounded by a layer of myoepithelial cells (arrowhead), arranged in a chondromyxoid stroma (triangle).

Figure 2C: Mucoepidermoid carcinoma: This cystic tumor has a mixed population of cells, with 3 distinct cell types—mucin producing cells (arrow), squamoid cells (arrowhead), and intermediate cells (triangle).

What Is the Expected Outcome After Superficial Parotidectomy to Excise the Patient's Warthin Tumor?

Surgical excision of Warthin tumor is curative, and we expect the patient to have a good clinical outcome. The risk of local recurrence after complete surgical excision is less than 2%.

The other tumors on our initial differential behave quite differently. Pleomorphic adenoma is also benign but has a higher local recurrence rate of up to 5% if treated by parotidectomy, and up to 25% if treated with simple enucleation. The behavior of mucoepidermoid carcinoma depends on the grade of the neoplasm. Local recurrence rates range from 15% to 30%, and 5-year survival ranges from 50% to 90%.[1,2]

Teaching Points

1. Salivary gland neoplasms are rare, accounting for less than 2% of all tumors.
2. Up to 80% of salivary gland neoplasms occur in the parotid gland, and up to 70% of parotid gland tumors are benign.
3. The likelihood of malignancy in each salivary gland in increasing order is: parotid gland, submandibular gland, minor salivary gland, and sublingual gland.
4. Clinical features are not definitively diagnostic of a benign or malignant process. Malignant tumors are suggested by rapid growth, pain, immobility, skin changes and facial asymmetry, cervical lymphadenopathy, and loss of nerve function. Benign tumors are suggested by absence of pain, mobility, slow growth, absence of nerve involvement.

5. Radiologic studies can provide important clues to the nature of a salivary gland tumor, including invasion beyond salivary gland parenchyma into adjacent structures and local lymphatic spread.
6. Fine needle aspiration biopsy of salivary gland tumors is an important initial diagnostic test that can frequently give an accurate diagnosis. When a specific diagnosis cannot be rendered, cytologic analysis can give a differential diagnosis that helps guide clinical/surgical management.
7. The 3 most common salivary gland tumors (pleomorphic adenoma, Warthin tumor, and mucoepidermoid carcinoma) have distinct cytologic and histologic appearances.
8. The most common salivary gland neoplasm is pleomorphic adenoma, a benign tumor that typically presents in the mid-40s and has a female predilection.
9. The second most common benign salivary gland neoplasm is Warthin tumor, which commonly presents in male smokers in their mid-60s. On physical examination, it has a "doughy" texture and can be multifocal or occur bilaterally. On aspiration, it produces a "motor oil" like fluid.
10. The most common malignant salivary gland neoplasm is mucoepidermoid carcinoma. It occurs over a broad age range and is the most common salivary gland malignancy in adults and children.
11. Pleomorphic adenoma and Warthin tumor can both be treated by surgical excision alone and have less than 5% risk of local recurrence.
12. The treatment and outcome of mucoepidermoid carcinoma is dependent on the tumor grade. High-grade tumors may require surgery and adjuvant radiation therapy, with local recurrence rate as high as 30%, and 5-year survival of 50%.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Educational Case: Medullary Thyroid Carcinoma

Carl T. McGary, MD, PhD[1]

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, cytology diagnostic certainty, endocrine, endocrine neoplasms, fine needle aspiration cytology, medullary thyroid carcinoma

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Primary Objective

EN5.2: Medullary Thyroid Carcinoma. Describe the molecular basis and clinicopathologic features of medullary thyroid carcinoma.

Competency 2: Organ System Pathology; Topic EN: Endocrine; Learning Goal 5: Endocrine Neoplasms.

Secondary Objective

CYP1.2: Categorizing Diagnostic Certainty. Compare and contrast the degree of diagnostic certainty applied to general categorization in cytologic diagnosis.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic CYP: Cytopathology; Learning Goal 1: Cytologic Diagnosis.

Patient Presentation

A 52-year-old Caucasian male presents to family medicine with an irregular 4-cm palpable nodule in the mid right thyroid lobe. He has no significant past medical history other than occasional diarrhea. Complete head and neck examination reveals no additional palpable nodules in the thyroid gland and no palpable adenopathy. The differential diagnosis for a palpable thyroid nodule includes a variety of benign and malignant entities, including colloid nodule, nodular hyperplasia, follicular thyroid adenoma, follicular thyroid carcinoma, papillary thyroid carcinoma (PTC), medullary thyroid carcinoma (MTC), anaplastic thyroid carcinoma, and lymphoma. The patient is referred to the lab for pathologist to perform fine needle aspiration (FNA) cytology of the nodule.

Diagnostic Findings, Part 1

The pathologist performs 3 FNA passes into the nodule under direct guidance using 25-gauge needles without suction, and the initial smears show adequate cellularity (Figure 1). Additional passes are not performed for cell block preparation. Using The Bethesda System for Reporting Thyroid Cytology, the pathologist finalizes the report as Bethesda category V, suspicious for malignancy and MTC. The cytology findings are shown in Figures 1 and 2 and compared to the more common PTC in Figure 3. The patient is referred to endocrinology for further evaluation.

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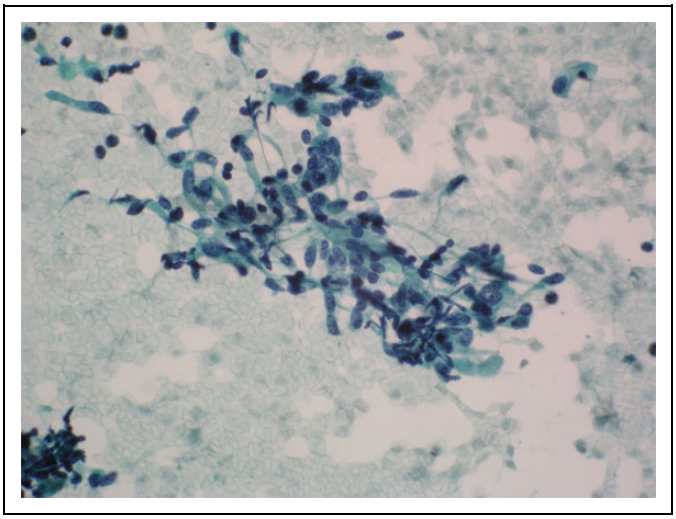

Figure 1. Papanicolaou stain at ×200 of the initial FNA smear showing background red blood cells, scant colloid, and a mixed population of neoplastic cells showing epithelioid and spindle cell morphology. Nuclear chromatin shows a "'salt and pepper" granularity and lacks features of papillary carcinoma (Figure 3), and the cell cytoplasm is somewhat granular. FNA indicates fine needle aspiration cytology.

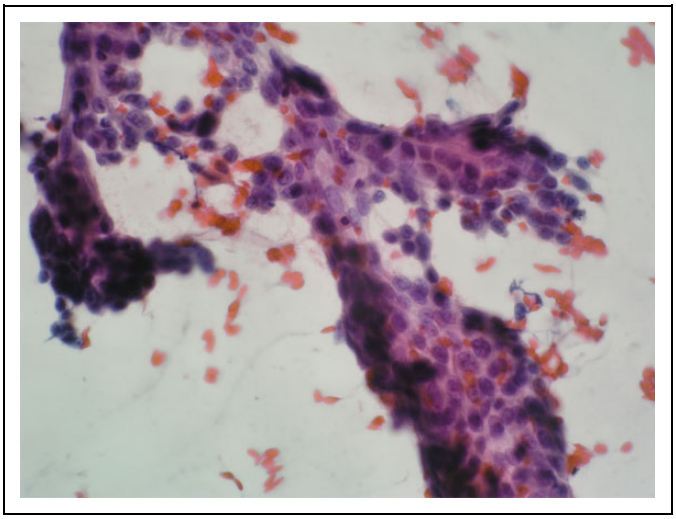

Figure 3. Papanicolaou stain of PTC for comparison with the patients with FNA cytology. Papillary thyroid carcinoma shows nongranular chromatin, nuclear grooves, small peripheral nucleoli, and occasional intranuclear pseudo-inclusions. Papillary-shaped irregular branching groups are also present. FNA indicates fine needle aspiration cytology; PTC, papillary thyroid carcinoma.

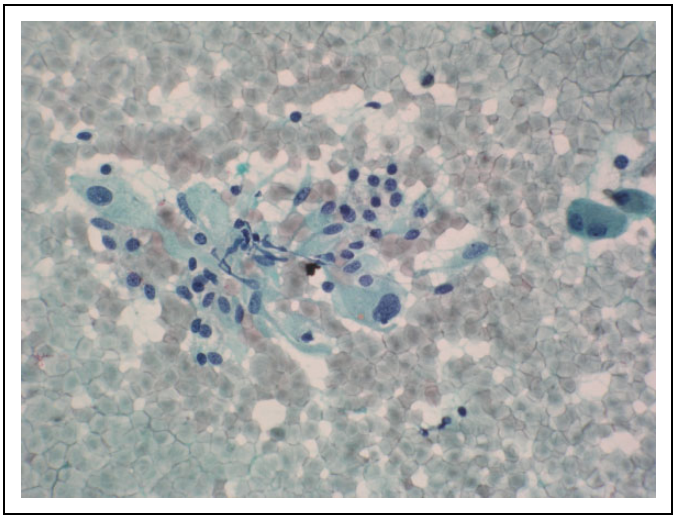

Figure 2. Papanicolaou stain at ×400 highlighting random nuclear atypia often seen in neuroendocrine neoplasia, as well as the granular cytoplasm and fine-to-coarse nuclear chromatin of medullary thyroid carcinoma.

Questions/Discussion Points, Part 1

Categorizing Diagnostic Certainty: Based on the Pathologist's Interpretation of the FNA, How Statistically Likely is the Patient to Harbor a Malignant Neoplasm and What is the Uncertainty of the Diagnosis?

The major categories used in diagnostic cytopathology include unsatisfactory for diagnosis, negative for malignancy, atypical cells present, suspicious for malignancy, and positive for malignancy. Each category carries an implied degree of certainty with regard to the pathology present. Diagnostic modifiers are also used in surgical pathology to suggest degrees of uncertainty, including "cannot rule out," "suggestive of," "consistent with," and "diagnostic of," in increasing order of certainty.[1] The issue of uncertainty in anatomic pathology diagnosis is highlighted by the presence of both interobserver (2 observers arriving at a different diagnosis on the same case) and intraobserver (the same observer arriving at different diagnoses on the same case at different times) diagnostic variation.[2]

Interinstitutional review of 777 patient specimens revealed a diagnostic difference in 71 specimens on review at the second institution. In 45 of the 71 discrepant specimens, the change in diagnosis led to altered therapy. The discordant diagnoses were significantly more common in cytology specimens (21%) than surgical specimens (7.8%), suggesting that cytologic diagnosis was more prone to uncertainty than histologic diagnosis.[3]

Historically, cytopathologists at different institutions have utilized somewhat different diagnostic terminology when reporting results of thyroid FNA. To address the variety of reporting systems and the resulting inherent confusion, the National Cancer Institute (NCI) hosted the NCI Thyroid FNA State of the Science Conference. The conference conclusions led to the publication of the Bethesda System for Reporting Thyroid Cytology,[4] which is now in wide use. Similar issues led to publication of the Paris System for Reporting Urinary Cytology.[5]

The Bethesda System for Reporting Thyroid Cytology[4] contains 6 general diagnostic categories, each with a specific given risk of underlying malignancy as shown in Table 1. The least amount of uncertainty is associated with the benign and malignant categories as these have the narrowest range for underlying malignancy. The greatest degree of uncertainty lies with the atypical category which shows the widest range for underlying

Table 1. Major Diagnostic Categories of The Bethesda System for Reporting Thyroid Cytology and the Associated Risk of Malignancy.

Diagnostic Category	Underlying Risk of Malignancy (%)
ND/unsatisfactory (I)	1-4
Benign (II)	0-3
AUS/FLUS (III)	5-15
FN/SFN (IV)	15-30
Suspicious for malignancy (V)	60-75
Malignant (VI)	97-99

Abbreviations: AUS, atypia of uncertain significance; FLUS, follicular lesion of uncertain significance; FN, follicular neoplasm; ND, nondiagnostic; SFN, suspicious for follicular neoplasm.

Table 2. Diagnostic Categories of The Paris System for Reporting Urinary Cytology and the Associated Risk of Malignancy.

Diagnostic Category	Underlying Risk of Malignancy (%)
Unsatisfactory	<5-10
Negative for HGUC	0-10
Atypical urothelial cells	8-35
Suspicious for HGUC	50-90
Low-grade urothelial neoplasm	~10
Positive for HGUC	>90
Positive for other malignancy	>90

Abbreviation: HGUC, high-grade urothelial carcinoma.

malignancy, and the suspicious category being between atypical and benign/malignant in terms of uncertainty. Thyroid FNA is somewhat unique in having 2 suspicious categories. Suspicious for follicular neoplasm less commonly has an underlying malignancy when compared to the suspicious for malignancy category, as the majority of follicular neoplasms are benign adenomas, rather than follicular carcinomas.

Similar uncertainty is seen in other types of cytology specimens, such as urine cytology using The Paris System for Reporting.[5] The risk of underlying malignancy in urine cytology based on The Paris System reporting is shown in Table 2. The wider the range for underlying malignancy, the greater the uncertainty for that diagnostic category.

In general, both benign and malignant cytologic diagnostic categories have the least associated uncertainty, and the most significant uncertainty is in the atypical category, with the suspicious category intermediate for the associated degree of uncertainty. Currently available molecular tests are available for use on ambiguous thyroid FNAs, to identify malignancy-associated genetic changes. These serve to decrease the broad diagnostic uncertainty in the atypical follicular cells of uncertain significance category and help direct treatment decisions (surgery vs continued clinical observation).

Diagnostic Findings, Part 2

The endocrinologist does a typical thyroid endocrine workup and finds that the patient is euthyroid and has a normal calcium.

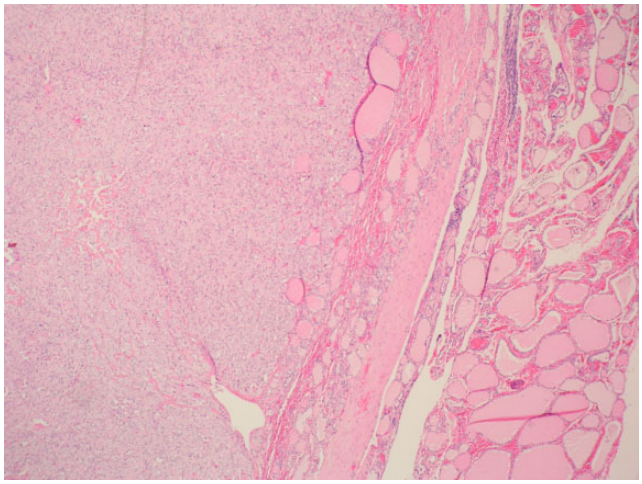

Figure 4. Hematoxylin and eosin stained section of the tumor thyroid interface at ×40 showing a well-circumscribed cellular neoplasm on the left without follicular or papillary architecture. The tumor was incompletely encapsulated, and entrapped benign follicles are seen at the periphery. The adjacent thyroid tissue showed no evidence of C-cell hyperplasia and contains medium-to-large colloid-filled follicles on the right.

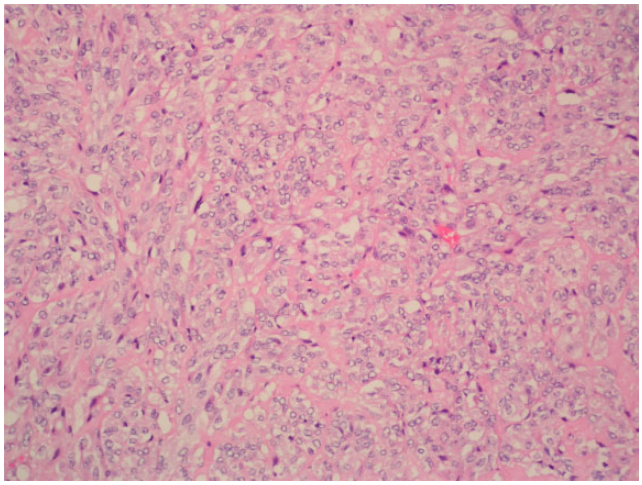

Figure 5. Hematoxylin and eosin stained section of tumor at ×200 showing mixed epithelioid and spindled morphology with only vague nesting of tumor cells and a majority diffuse growth pattern. Amyloid was not present.

Because of the suspicion of MTC on the FNA, he also performs a serum calcitonin that comes back as 5679 pg/mL (normal <10 pg/mL). The patient is referred to otolaryngology and a total thyroidectomy and central and bilateral node dissection is performed. The final pathology shows a 3.9-cm medullary carcinoma (Figures 4-6) confined to the thyroid gland with 3 of 6 central nodes microscopically involved and none of 13 right and 1 of 11 left neck nodes involved by medullary carcinoma. The pathologic stage is reported as pT2, pN1a, pM-not applicable, or stage group III.

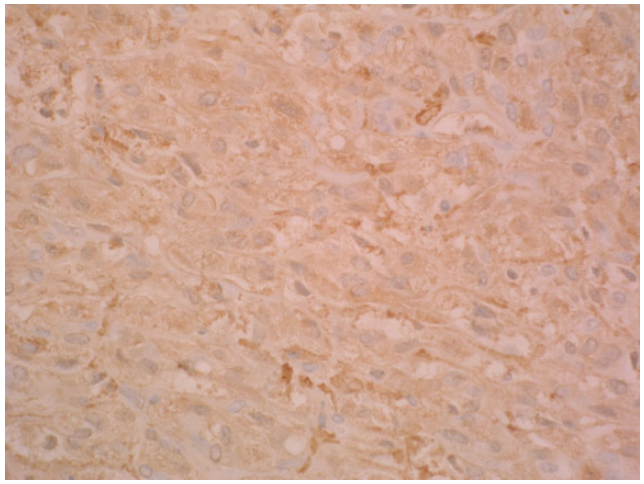

Figure 6. Immunochemistry of tumor for calcitonin ×400 showing diffuse granular cytoplasmic staining.

Questions/Discussion Points, Part 2

What Clinicopathologic Features are Common in Both Sporadic and Inherited Medullary Thyroid Carcinoma?

Medullary thyroid carcinoma is a primary tumor of the thyroid gland which shows differentiation along the lines of thyroid parafollicular C cells.[6-8] Medullary thyroid carcinoma typically secretes calcitonin, although nonsecretory tumors occur rarely. Serum calcitonin reflects quantity of tumor present, except in nonsecreting patients. Medullary thyroid carcinoma is almost always carcinoembryonic antigen (CEA) positive, and in noncalcitonin-secreting tumors, serum CEA levels can be followed, similar to calcitonin levels in secreting tumors to assess disease burden and therapeutic response. Even though elevated calcitonin levels are present, serum calcium is not typically decreased below normal levels. Medullary thyroid carcinoma tumors sometimes secrete other hormones, such as adrenal corticotropic hormone, serotonin, and vasoactive intestinal peptide (VIP), which can result in a paraneoplastic presentation such as diarrhea if VIP secretion occurs. The VIP levels were not measured in this patient, and it is not clear whether his intermittent diarrhea was related to the MTC. Medullary thyroid carcinomas are relatively uncommon tumors accounting for less than 2% to 3% of thyroid neoplasia.

Medullary thyroid carcinoma can present as a sporadic tumor or as part of an inherited tumor syndrome. The histology of MTC is quite variable, but in general is not distinct for sporadic or inherited cases. A mixture of spindled and epithelioid cells is common, and plasmacytoid morphology is often seen. Neuroendocrine features include finely granular cytoplasm due to variable presence of neurosecretory granules. The chromatin is mixed fine and coarse and classically described as "salt and pepper" chromatin which is commonly seen in neuroendocrine tumors. Cells can be arranged in sheets, nested aggregates, trabeculae, or even follicles, and mitotic figures tend to be sparse. These features of MTC contrast with the more common PTC (Figure 3). Nuclear features of PTC include pale nongranular nuclear chromatin, nuclear grooves, nuclear pseudoinclusions, and small peripheral nucleoli. Amyloid deposition is commonly present in up to 90% of cases, but was absent in this particular case, and is composed of calcitonin peptides. Immunochemistry shows positive granular cytoplasmic staining for calcitonin in the tumor cells and diffusely stains the amyloid deposits. Immunochemistry is also positive for other neuroendocrine markers, such as chromogranin and synaptophysin. Cytologic atypia ranges from minimal, to focal, to widespread.

Describe the Features Unique to Sporadic Medullary Thyroid Carcinoma

Medullary thyroid carcinoma occurs as sporadic disease in 70% of cases, and the sporadic cases present typically as a neck mass, as in this case, but clinical findings may also include dysphagia and/or hoarseness. When MTC presents as a neck mass, nodal involvement is relatively frequent (~70%) and non-nodal metastasis (10%) also occurs. Sporadic cases show a slight female predominance and are seen predominantly in the fifth and sixth decades. These are usually unilateral and unifocal tumors of the thyroid. Unlike PTC, ionizing radiation exposure does not seem to be etiologically involved in sporadic MTC.

Describe the Features Unique to Inherited Medullary Thyroid Carcinoma

Familial cases occur as part of inherited syndromes in 30% of cases (multiple endocrine neoplasia type 2A [MEN-2A] or MEN-2B or familial medullary thyroid carcinoma [FMTC]) and are often associated with other endocrine neoplasms. Medullary thyroid carcinoma in this setting may present either as a result of endocrine disease in other organs or with symptoms in the neck. Familial/inherited cases present at younger ages than do sporadic cases. Medullary thyroid carcinoma in the setting of MEN-2B more commonly metastasizes than what is seen in MEN-2A, FMTC, or sporadic disease. Bilateral thyroid involvement and multifocal disease are more common in inherited MTC than in sporadic disease. Penetrance of medullary thyroid cancer development is age and mutation dependent; however, MTC inevitably develops in MEN-2 with *RET* mutations, and early total thyroidectomy is preventative. Early onset is typical in MEN-2B with later onset in MEN-2A. Thyroid tissue outside the tumor in inherited cases typically shows background C cell hyperplasia.

Describe the Molecular Basis of Sporadic Medullary Thyroid Carcinoma

Activating somatic point mutations of the *RET* proto-oncogene are noted in sporadic medullary carcinoma in approximately 40% to 60% of cases. The most frequently seen mutation in

sporadic cases is the M918T mutation in exon 16. Interestingly, this is also the same mutation as the germline mutation in the vast majority of MEN-2B patients. *RAS* mutations are also seen in some sporadic cases, usually those that are *RET* mutation negative. Thus, in sporadic disease, *RAS* and *RET* mutations commonly show mutual exclusion.

Describe the Molecular Basis of Inherited Medullary Thyroid Carcinoma

Germline mutation of the *RET* proto-oncogene with gain of function is the underlying feature in inherited MTC, as seen in MEN-2A, MEN-2B, and FMTC (a variant of MEN-2A). The *RET* proto-oncogene codes for a receptor tyrosine kinase that binds glial-derived neurotrophic factor and similar ligands. Ligand binding to receptor leads to intracellular growth signals as well as signals for differentiation. Various specific *RET* mutations occur in MEN-2A, and coexisting parathyroid hyperplasia and pheochromocytoma are characteristic. The specific *RET* mutations in MEN-2B are associated with pheochromocytoma as well; however, the hyperparathyroidism is absent.

Teaching Points

- Major cytologic diagnostic categories (nondiagnostic, benign, suspicious, and malignant) each carry an associated risk of underlying malignancy and uncertainty, which have been published for various types of specimens.
- Cytologic diagnostic categories of benign and malignant have the least amount of associated diagnostic uncertainty and the atypical category the highest.
- Medullary thyroid carcinoma is a neuroendocrine tumor showing C-cell differentiation.
- Medullary thyroid carcinoma is immunochemically positive for calcitonin (which is elevated in serum, except in rare nonsecreting cases), chromogranin, synaptophysin, and CEA.
- Medullary thyroid carcinoma can be followed clinically with serum calcitonin or CEA, and CEA is helpful in calcitonin nonsecreting cases.
- Occasionally, MTCs secrete other hormones and may have paraneoplastic presentations, for example, VIP—diarrhea.
- Medullary thyroid carcinoma can be sporadic or inherited.
- Sporadic and inherited MTCs have the same histologic spectrum with amyloid deposition, sporadic disease typically being unilateral and unifocal and inherited disease more likely to be bilateral and multifocal.
- Inherited MTC shows C-cell hyperplasia in the nonneoplastic thyroid tissue.
- Specific genetic and molecular mechanisms underlie both sporadic and inherited medullary thyroid cancer, with the *RET* gene being most frequently involved.
- The inevitable development of medullary thyroid cancer associated with MEN-2 can be prevented by early prophylactic total thyroidectomy.

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Educational Case: Bladder Carcinoma In Situ

H. James Williams, MD[1]

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, bladder neoplasia, bladder washings, carcinoma in situ (CIS) of the urinary bladder, FISH, screening urine cytology, voided urine cytology

Received April 30, 2017. Received revised May 31, 2017. Accepted for publication June 14, 2017.

Primary Objective

Objective UTB1.3: Diagnosis and Surveillance of Urothelial Carcinoma. Describe the typical clinical presentation of urothelial carcinoma and the advantages and limitations of urine cytology in diagnosis and surveillance of urothelial carcinoma.

Competency 2: Organ System Pathology; Topic UTB: Bladder; Learning Goal 1: Bladder Neoplasia.

Patient Presentation

A 57-year-old man presents with a complaint of cramping pain on urination (dysuria) and red coloration of his urine (gross hematuria).

On physical examination, the patient has vague abdominopelvic discomfort on compression with no palpable mass. The physical examination was otherwise unremarkable, and the patient is afebrile.

Diagnostic Findings

Initial laboratory tests revealed a urinalysis with numerous red blood cells and rare white blood cells, a negative urine culture, normal complete blood cell count, and a normal serum creatinine level.

Questions/Discussion Points

What pertinent questions would you ask the patient?

How long have these symptoms been present?
Have they been decreasing or increasing in severity?
Are there difficulties passing urine or associated burning?
Have you passed any stones, clots, or tissues?
Have you ever had these symptoms before?
Are you a smoker?
What kind of work do you do and have you had different jobs in the past?
Do you take any medications?
Have you ever been diagnosed with a malignancy?
Is there a family history of cancer and, if so, what kind?

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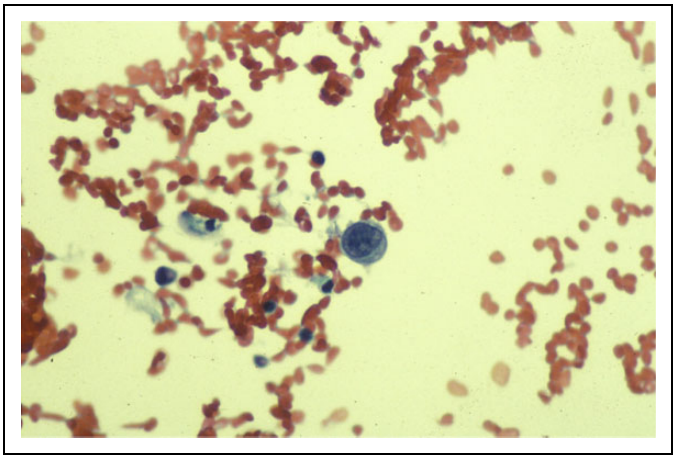

Figure 1. Urine cytology.

What additional laboratory test(s) would you consider at this point?

Urine cytology (see Figure 1).

Describe the findings on voided urine cytology (see Figure 1). What is your diagnosis?

There is a single cell with markedly enlarged hyperchromatic nuclei with irregular borders and high N/C ratio in a background of blood. Voided urine normally is hypocellular with few single benign urothelial cells and inflammatory cells. The presence of cohesive groups of cytologically bland urothelial cells in a voided urine is considered an abnormal finding that may be associated with stones, UTI, recent instrumentation, or low-grade papillary neoplasm.[2] In contrast, the presence of cohesive groups of cytologically bland urothelial cells in a bladder washing is a common finding due to instrumentation and mechanical dislodging of cells from the washing pressure. While this may raise concern for a low-grade papillary lesion on cytology, clinically it is not an issue as a papillary lesion would be seen and biopsied on cystoscopy. Bladder washings are useful for detecting flat CIS when there is not a papillary lesion seen on cystoscopy. Flat CIS as seen on urine cytology (voided or washings) has high-grade cytologic features as seen in this exercise.

The diagnosis is: positive for malignant cells, high-grade urothelial carcinoma.

What would be your next step?

The patient is referred to an urologist who performs cystoscopy. On cystoscopy, no discrete lesions or masses are seen. There are several erythematous (reddened) patchy areas which are biopsied and a bladder washing is obtained. Describe the cytologic findings in the bladder washing (see Figure 2).

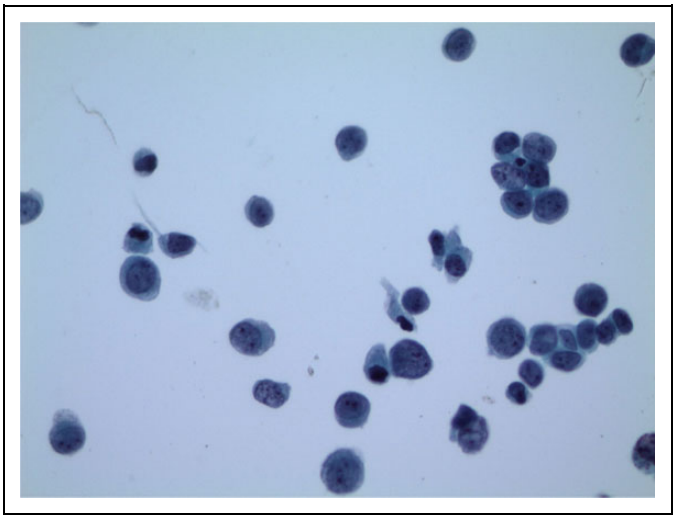

Figure 2. Bladder washing cytology.

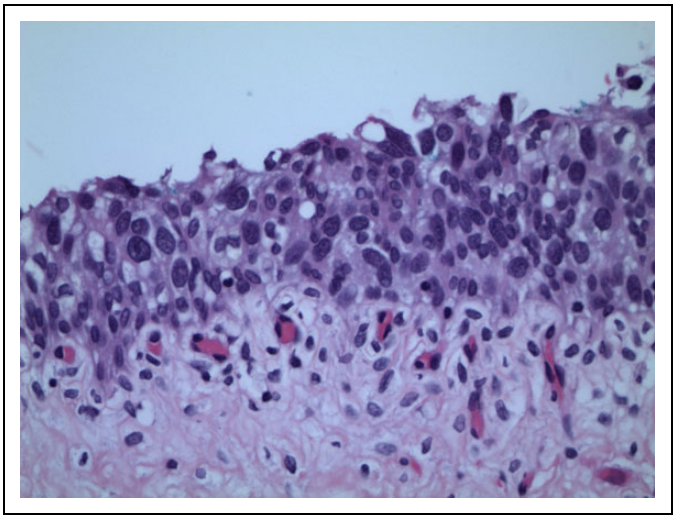

Figure 3. Bladder biopsy from an erythematous patch seen on cystoscopy.

How would you explain these findings in the absence of an identifiable mass on cystoscopy?

In the absence of a discrete lesion/mass in the bladder, the possibility the malignant cells could be arising in the renal pelvis or ureters should be considered.

Describe the histologic findings in the bladder biopsy taken from one of the erythematous patches seen on cystoscopy (see Figure 3). What is your diagnosis?

Carcinoma in situ (CIS) of the urinary bladder. The bladder washing has numerous single discohesive cells similar to that seen in the voided urine sample. In the bladder biopsy the urothelium is replaced by disorganized cells with enlarged hyperchromatic nuclei with increased N/C ratio and occasional

mitoses. Note the basement membrane is intact with no evidence of invasion of the underlying stroma.

In addition to aiding in the primary diagnosis of urinary malignancies, what other use is there for urine cytology?

Once a patient has been diagnosed and treated for an urothelial malignancy, the patient is at risk of recurrence or development of additional urothelial malignancies. In addition to periodic cystoscopy, urine cytologies are a useful screening test to detect a recurrent or new malignancy. As an adjuvant study, fluorescence in situ hybridization can be performed on the urine specimen looking for chromosomal abnormalities (aneuploidy of chromosomes 3, 7, and 17 and 9p deletions).[1]

Teaching Points

- Bladder CIS can present with irritative bladder symptoms (dysuria, nocturia, urinary frequency) or hematuria. Other clinical possibilities for patients with these symptoms include urinary tract infection (UTI), interstitial cystitis, prostatitis (in men), and renal stones. Particularly, in older patients, the possibility of an urothelial malignancy should be considered.
- High-grade urothelial carcinoma can be identified in voided urine; however, it does not distinguish between flat in situ carcinoma versus a papillary urothelial neoplasm.
- Voided urine normally is hypocellular with few single benign urothelial cells and inflammatory cells. The presence of cohesive groups of cytologically bland urothelial cells in a voided urine may be associated with stones, UTI, recent instrumentation, or low-grade papillary neoplasm.[2]
- The presence of cohesive groups of cytologically bland urothelial cells in a bladder washing is a common finding due to instrumentation and mechanical dislodging of cells.
- Bladder washings are useful for detecting flat CIS when there is not a papillary lesion seen on cystoscopy. Flat CIS as seen on urine cytology (voided or washings) has high-grade cytologic features as seen in this exercise.
- Urine cytology is an important means of follow-up surveillance in patients who have had urothelial malignancy.

Declaration of Conflicting Interests

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Autosomal Recessive Polycystic Kidney Disease

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, autosomal recessive, cystic disorders, congenital, kidney, oligohydramnios

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Primary Objective

Objective UTK4.1: Inherited Renal Disorders. Compare autosomal dominant and autosomal recessive polycystic kidney disease in terms of pathological anatomy, molecular pathogenesis, and clinical presentation.

Competency 2: Organ System Pathology; Topic UTK: Kidney; Learning Goal 4: Congenital Disorders of the Kidney.

Patient Presentation

A 25-year-old G1 woman with no prenatal care presents to her physician with absent fetal movement. A diagnosis of in utero fetal demise is made. The third trimester infant shown was delivered (Figure 1). Significant oligohydramnios was noted at delivery.

Diagnostic Findings

An autopsy performed on the stillborn infant showed marked enlargement of the kidneys (combined weight of 105 g vs expected of 20.8 g) and the following changes on gross and microscopic examination in addition to pulmonary hypoplasia (combined lung weight of 20 g vs expected of 43 g) (Figure 2).

Questions/Discussion Points

What is the Differential Diagnosis for Oligohydramnios?

The infant shows the classic features of oligohydramnios sequence, also called Potter sequence. This sequence includes limb deformities, such as clubbed feet and hip deformities, craniofacial anomalies, such as flattened ears and nose, hypoplastic mandible and epicanthal malformations, and pulmonary hypoplasia.[1] The differential diagnosis of oligohydramnios consists of bilateral renal agenesis, autosomal recessive polycystic kidney disease (ARPKD), bilateral cystic renal dysplasia, obstructive uropathy, and chronic loss of amniotic fluid.[2]

Describe the Gross and Microscopic Pathologic Features Observed in the Kidneys at Autopsy

Grossly, the kidneys are massively enlarged with a reniform appearance. On sectioning, the kidneys show cystic dilation of

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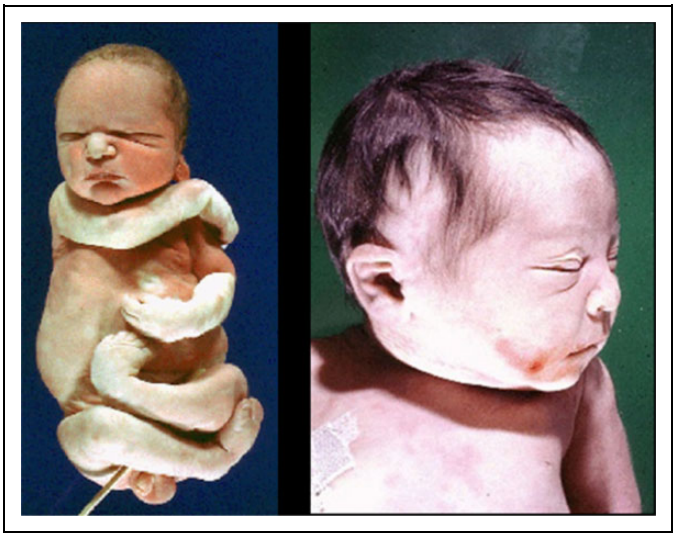

Figure 1. Infant with oligohydramnios (Potter) sequence. The left image shows a third trimester infant with flexion of the upper and lower extremities and spade-like hands and feet with abnormal facies. The right image shows the characteristic facial features of beaked nose, low-set flattened ears, prominent epicanthal folds, and receding chin.

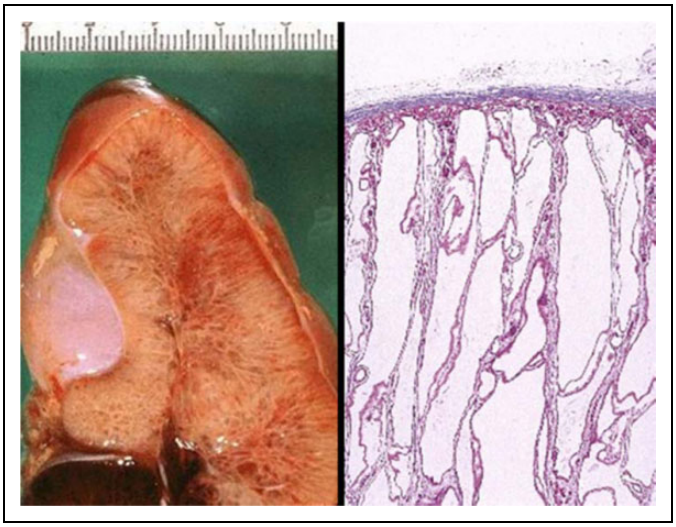

Figure 2. Gross appearance of kidney demonstrating cystic dilation of collecting ducts. Left: Medium power H&E stain of renal parenchyma illustrating cystic dilation of collecting ducts. Right: The long axis of the cysts is perpendicular to the connective tissue capsule. Normal glomeruli can be seen between collecting ducts.

the collecting ducts demonstrating a radial pattern. On microscopic examination, the collecting ducts are cystically dilated with the long axis of the cyst perpendicular to the capsule. Glomeruli and tubules may be seen between the collecting ducts.[2]

What is the Diagnosis Based on the Autopsy Findings?

The gross and histologic appearance of the kidneys is consistent with ARPKD.

Outline the Etiology and Pathogenesis of Autosomal Recessive Polycystic Kidney Disease

Autosomal recessive polycystic kidney disease has an estimated incidence between 1:10 000 and 1:40 000.[3] Neither race nor gender has been linked to increased prevalence.[4] Different clinical presentations are observed. Fetal demise or death within the first year of life occurs in 30% of patients. Those who survive through infancy go on to develop progressive renal failure and liver disease leading to portal hypertension.[5]

Autosomal recessive polycystic kidney disease is due to a mutation in the *PKHD1* gene on chromosome 6 that codes for the protein fibrocystin.[2] There have been more than 750 *PKHD1* mutations identified, the most common mutation of which is a missense mutation on exon 3 that accounts for more than 20% of cases.[6] Most cases are familial, but de novo mutations are possible and account for 2 to 5% of cases.[7] Diagnostic DNA testing is available for some of the most common causative mutations but is often not needed due to characteristic phenotypic and histologic findings. Genetic testing can be useful when the diagnosis is considered prenatally.[8]

Fibrocystin is a protein highly expressed in the primary cilia lining the collecting ducts of the kidney, the bile ducts, and pancreatic ducts. Abnormal expression of fibrocystin leads to defective intracellular signaling of epithelial cells during development of the kidney and biliary tract leading to cystic dilation of the collecting ducts and ductal plate malformations in the biliary tree. Defective remodeling of the ductal plate during development leading to dilation of the bile ducts and accompanied by increased periductal fibrosis may eventually lead to portal hypertension.[8]

Pulmonary hypoplasia is a complication of ARPKD. Several factors are involved. Decreased amniotic fluid affects the expansion of the lungs in utero. External compression of the fetus by the uterine wall secondary to oligohydramnios and the enlargement of the kidneys pushing up on the diaphragm decrease the thoracic cavity volume contributing to the pulmonary hypoplasia.

Contrast Autosomal Recessive Polycystic Kidney Disease With Autosomal Dominant Polycystic Kidney Disease

In contrast to ARPKD, autosomal dominant polycystic kidney (ADPKD) is most frequently due to a mutation in the *PKD1* gene (chromosome 16) or the *PKD2* gene (chromosome 4) that codes for the proteins polycystin-1 and polycystin-2 (Table 1). These proteins are also involved with ciliary function and intercellular signaling during development. Primary cilia are thought to have both chemoreceptor and mechanoreceptor functions and play a role in cell growth. Autosomal dominant polycystic kidney disease is observed in 1/400 to 1/1000 live births and accounts for about 10% of renal transplants. Most patients are asymptomatic early in life and present in middle age with chronic renal failure. Manifestations include hematuria, proteinuria, and hypertension. A small percentage of cases are associated with intracranial berry aneurysms

Table 1. Comparison of ARPKD with ADPKD.

Feature	ARPKD	ADPKD
Incidence	1:10 000 to 1:40 000	1:400 to 1:1 000
Involved gene(s)	*PKHD1* on chromosome 6	*PKD1* on chromosome 16 *PKD2* on chromosome 4
Protein defects	Fibrocystin	Polycystin-1 Polycystin-2
Histologic appearance	Diffuse cystic dilation of the collecting ducts with the long axis of the cyst perpendicular to the capsule	Haphazardly arranged, cystic dilation of all parts of the involved nephron with normal renal parenchyma interspersed
Age at symptom onset	Infancy	Middle-aged adulthood
Complications	In utero fetal demise Neonatal respiratory distress Renal failure Liver failure	Renal failure Rupture of berry aneurysms

Abbreviations: ARPKD, Autosomal recessive polycystic kidney disease; ADPKD, Autosomal dominant polycystic kidney disease.

as well as mitral valve prolapse and hepatic cysts. Grossly, the kidneys are enlarged and may weigh up to 4 kg (normal kidney weight 120-170 g). On sectioning, cysts up to 3 to 4 cm in diameter are haphazardly distributed throughout the renal parenchyma. On microscopic examination, all parts of the nephron may be cystically dilated. Normal renal parenchyma may be seen between cysts.[2]

Teaching Points

- Oligohydramnios (Potter) sequence is defined as the presence of clubbed feet, craniofacial anomalies, and pulmonary hypoplasia in the setting of a below normal volume of amniotic fluid[1]:
- Autosomal recessive polycystic kidney disease should be considered in the differential diagnosis for any patient presenting with oligohydramnios.[2]
- In ARPKD, the characteristic histologic appearance of the kidneys includes large, cystic dilations that are oriented with the long axis perpendicular to the renal capsule and represent dilations of the collecting ducts.[2]
- Thirty percent of affected patients die prenatally or within the first year of life. Patients surviving past the first year of life may go on to develop progressive renal failure and liver disease.[8]
- Autosomal recessive polycystic kidney disease is due to abnormal expression of the *PKHD* gene on chromosome 6 that codes for fibrocystin. Abnormal fibrocystin results in defective intracellular signaling in utero, leading to the development of cystic dilations of the renal collecting ducts and biliary tree.[8]
- Autosomal dominant polycystic kidney disease is due to a mutation in *PKD1* gene on chromosome 16 or *PKD2* gene on chromosome 4. These genes code for polycystin-1 and polycystin-2, respectively, which are also involved in intracellular signaling in utero, as well as ciliary function.[2]
- Unlike ARPKD, ADPKD presents in middle age with hematuria, proteinuria, and hypertension, leading eventually to renal failure. Other conditions associated with ADPKD include intracranial berry aneurysms, mitral valve prolapse, and hepatic cysts.[2]
- The histologic appearance of ADPKD differs from ARPKD in that cystic areas are scattered throughout the renal parenchyma, without uniform orientation, and all parts of the nephron may be involved, instead of only the collecting duct as in ARPKD.[2]

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Squamous Cell Carcinoma of the Lung

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, morphologic features, paraneoplastic syndrome, pulmonary neoplasia, squamous cell carcinoma

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Primary Objective

Objective RS3.2: Morphologic Features of Lung Neoplasms. Discuss key gross and histopathologic features that may help differentiate between small cell, adenocarcinoma, and squamous cell carcinoma.

Competency 2: Organ System Pathology; Topic RS: Respiratory System; Learning Goal 3: Lung Neoplasia.

Secondary Objectives

Objective RS3.1: Lung Neoplasms. Describe the common locations for the different types of lung cancer.

Competency 2: Organ System Pathology; Topic RS: Respiratory System; Learning Goal 3: Lung Neoplasia.

Objective RS3.5: Environmental Factors Predisposing to Lung Cancer. Explain the environmental factors that predispose to the development of lung cancer and illustrate how these factors interact with genetic factors in the development of cancer.

Competency 2: Organ System Pathology; Topic RS: Respiratory System; Learning Goal 3: Lung Neoplasia.

Patient Presentation

A 62-year-old male presents to the clinic with a 4-month history of dysphagia to solids in addition to nausea and abdominal pain. In addition, he reports recent hemoptysis and the onset of hoarseness. He also has had unintentional 10-kg (22 lb) weight loss over the past 6 months. He has a history of emphysema. He takes no medication. He has a 26 pack-year history of cigarette smoking and has a 6-pack beer on weekends. Physical examination reveals a thin male who appears older than his stated age, oriented to time and place. Body mass index is 18. Vital signs are within normal limits. Chest auscultation reveals diminished breath sounds over the right lung fields.

Diagnostic Findings, Part 1

A chest X-ray reveals a 6-cm hilar mass on the right.

Laboratory studies show serum calcium 12 mg/dL (normal 8.5-10.5 mg/dL).

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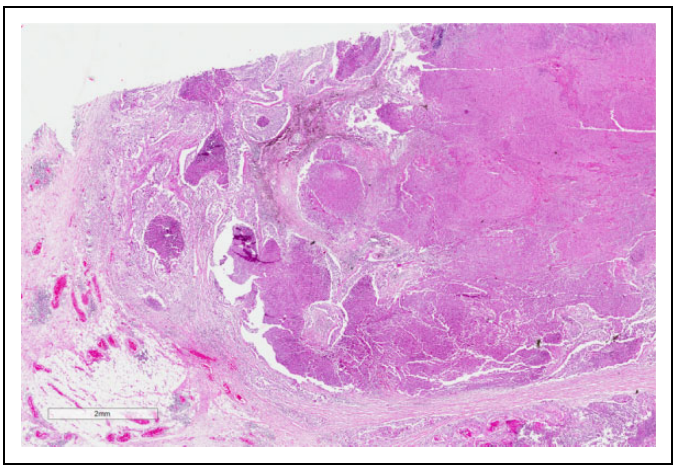

Figure 1. Histopathology of the lung biopsy. A low-power image showing extensive tumor on the right hand side, with nests of tumor cells infiltrating into the pulmonary parenchyma on the left.

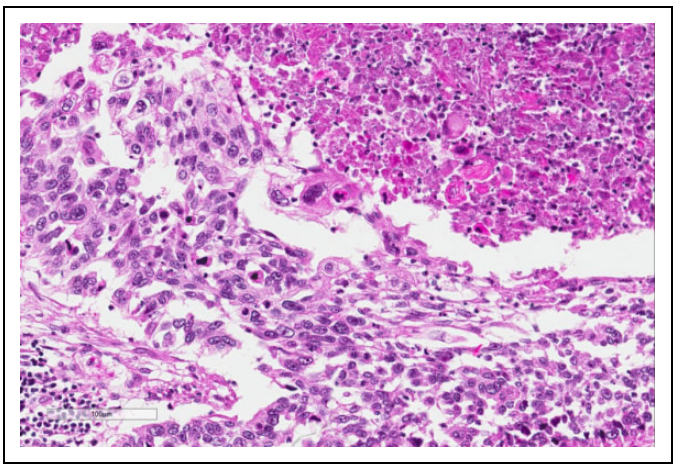

Figure 2. Higher power image of the tumor with neoplastic cells that have keratinization shown by brightly eosinophilic cytoplasm in the upper right hand side, while the neoplastic cells on the mid and left and lower image show pleomorphism and hyperchromasia.

Questions/Discussion Points, Part 1

What is Your Differential Diagnosis Based on the Clinical History?

The patient presents with dysphagia, hemoptysis, and hoarseness with a significant weight loss history, which could be indications of an upper airway neoplasm such as laryngeal carcinoma, esophageal carcinoma, or a lung carcinoma. The chest X-ray findings of a hilar mass would make a lung lesion (neoplasm or infection) most likely, or a middle mediastinum neoplasm such as lymphoma. Central lung neoplasms would include a differential of squamous cell carcinoma, small cell carcinoma, or a carcinoid tumor. Less likely, this could be an adenocarcinoma. The hypercalcemia may be indicative of a paraneoplastic syndrome due to squamous cell carcinoma.

What Further Testing is Indicated for this Patient?

A biopsy of the lesion is indicated to identify the origin of this mass.

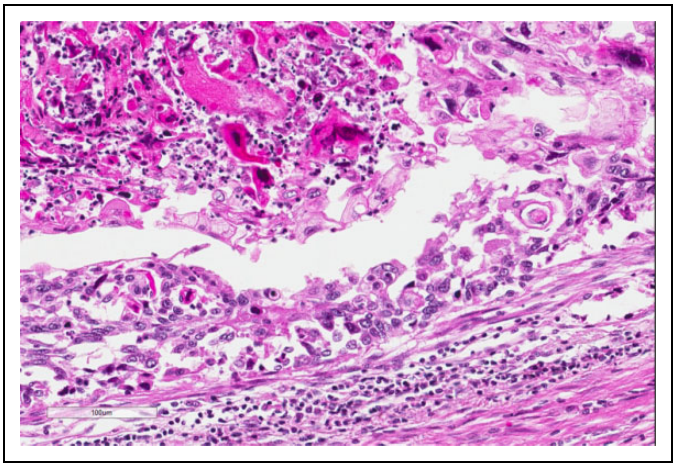

Figure 3. High power of another area of tumor cells showing many keratinized tumor cells that are hyperchromatic and eosinophilic.

Diagnostic Findings, Part 2

A biopsy was performed because of the high clinical suspicion of a malignant lesion. Figures 1 to 3 show representative histologic features of the biopsy on low, medium, and high power.

Questions/Discussion Points, Part 2

Describe the Histologic Heatures of Figures 1 to 3. Based on the Histologic Findings and Clinical Presentation, What is Your Diagnosis?

The diagnosis, based on the morphologic features, is squamous cell carcinoma. On low power, there are multiple infiltrating nests of tumor cells, as well as a large area of necrosis in the upper right corner (Figure 1). On intermediate magnification (Figure 2), one can recognize sheets of polygonal cells with a high nuclear to cytoplasmic ratio, hyperchromatic and pleomorphic nuclei on the bottom and left of the image, and large keratinizing and atypical cells within the necrotic area on the upper right. Keratinization can be in the form of keratin pearls or as deeply eosinophilic dyskeratotic malignant cells (Figure 3). If one observes intercellular bridges between the polygonal cells, this can be helpful in confirming squamous cell carcinoma.

Histologically one will find a progression of epithelial cells from normal respiratory bronchial epithelium to squamous metaplasia from the exposure of cigarette smoke. With time and continued exposure, the epithelium will progress to dysplasia, then carcinoma in situ, and finally, invasive squamous cell carcinoma once tumor cells have broken through the basement membrane.

Other common lung tumors include adenocarcinoma and small cell carcinoma. Adenocarcinoma has a glandular pattern, it often contains larger cells with lacy cytoplasm and large pleomorphic nuclei. These cells may produce mucin. The cells from small cell carcinoma are medium sized, with a high nuclear to cytoplasmic ratio, and have hyperchromatic nuclei with a granular or salt and pepper appearance. Since the small cells are deficient in intermediate filaments, they conform to the shape of adjoining cells in a pattern that is referred to as molding.

If the Tumor Spreads locally to the Recurrent Laryngeal Nerve, Which Clinical Feature would you Probably Elicit from the Patient History?

Local spread of lung tumors may produce multiple different clinical features depending on the structures that are affected by the invasion of the tumor. Over 50% of patients will present with a cough if the tumor involves the central airways. About 24% to 50% of patients will present with hemoptysis if there is hemorrhage secondary to tumor invasion in the airway. Patients may present with hoarseness if there is recurrent laryngeal nerve invasion or diaphragm paralysis with phrenic nerve invasion and pleural effusions with pleural invasion.[1]

Although Chronic Smoking is a Well-known Carcinogen Associated with Lung Cancer, Cancer Only Develops in 11% of Heavy Smokers. What Genetic Risk Factors Most Commonly Promote the Development of Squamous Cell Carcinoma within Heavy Smokers?

Carcinogenesis is the process by which normal cells are transformed in carcinoma. Multiple mutations accumulate over years of growth affecting many aspects of cell development and regulation until one or more clones emerge with all hallmarks of cancer. With continued tumor growth, cells compete for nutrients in the microenvironment, additional mutations accumulate, and progression leads to a genetically heterogeneous neoplasm.[2]

The duration and the amount of exposure to cigarette smoke are well associated with lung cancer risk. In cigarettes, particularly, there are multiple procarcinogens present, which can be converted to carcinogens via the P-450 monooxygenase system. Some patients with P-450 system polymorphisms have an even greater propensity to activate these cigarette smoke procarcinogens to carcinogens.

In addition, the normal mucosa cells of patients with lung squamous cell carcinoma frequently have tumor protein p53 (TP53) mutations. TP53 mutations are early events in the progression from in situ to invasive squamous cell carcinoma. TP53 mutations are found in 10% to 50% of the cells of squamous cell dysplasia and in 60% to 90% of carcinoma in situ cells.[3] TP53 mutations are also identified in 75% to 90% of small cell lung carcinoma cells.

Which of the Findings Described in the Patient Presentation Above is Most Closely Associated with the Specific Histologic Type of the Patient'S Tumor?

This patient exhibits symptoms of a paraneoplastic syndrome. Such syndromes arise when the cancer cells produce systemic effects by acquiring the ability to secrete hormones not usually associated with the tissue of origin. The process of why particular syndromes are often associated with particular cancers is not entirely understood.

Paraneoplastic syndromes are important to recognize for several reasons including: these may cause significant clinical consequences, such as hypercalcemia, these may be the first clinical sign of an underlying malignancy, or these may confuse the clinical picture. Hypercalcemia is a common paraneoplastic syndrome that can be seen with multiple different types of neoplasms including squamous cell carcinoma of the lung, breast carcinomas, renal cell carcinoma, ovarian neoplasm, or adult T-cell leukemia/lymphoma. The mechanism of the production of the paraneoplastic hypercalcemia is due to parathyroid hormone-related protein (PTHRP) production, which can be induced by the primary cancer or in the bone metastasis. Alternatively, it may be related to other factors secondary to the malignancy such as transforming growth factor α, tumor necrosis factor, or interleukin 1. Clinically, the hypercalcemia may present with nausea and vomiting in addition to abdominal cramps. Other hypercalcemia symptoms include constipation, frequent urination, and confusion.

Other common paraneoplastic syndromes include polycythemia secondary to erythropoietin production as seen in renal cell carcinoma, hypoglycemia due to insulin or insulin-like substance production as seen in ovarian carcinomas, or Cushing syndrome due to adrenocorticotropic hormone (ACTH) production as seen in small cell carcinoma of the lung.[4]

In Considering The General Category of Lung Neoplasms, How Does the Location of the Neoplasm in the Lungs Help You Narrow Your Differential of the Specific Type of Lung Cancer?

Common lung neoplasms have a predilection for specific areas of the lung. A central or hilar mass is most likely to be a squamous cell carcinoma or a small cell tumor, less commonly an adenocarcinoma. These have distinctive morphologies that are important to differentiate for adequate treatment. In addition, classifying a lung malignancy as adenocarcinoma has the added requirement for molecular testing to be performed in order to determine whether the patient is eligible for targeted therapy. If tumors arise in the periphery of the lungs, then they tend to be adenocarcinomas, especially if they arise at a previous scar site. Differentiating the exact cell type of a lung tumor is important for treatment considerations. Squamous cell carcinomas and adenocarcinomas tend to be treated with surgical resection as a primary treatment, while small cell carcinoma is treated with chemotherapy as a first line.

Teaching Points

- Squamous cell carcinoma is often a centrally located tumor close to the hilum.
- Histologic hallmarks of squamous cell carcinoma are polygonal cells with intercellular bridges, crisp eosinophilic cytoplasm. Tumors may also contain keratin pearls, and larger tumors may have extensive necrosis.
- The histologic progression of normal mucosa to squamous cell carcinoma includes normal respiratory epithelium, squamous metaplasia, dysplasia, carcinoma in situ, and then invasive squamous cell carcinoma once the basement membrane is breached.
- Squamous cell carcinoma may present with hypercalcemia in a paraneoplastic syndrome due to PTHRP production.
- Adenocarcinoma of the lung is often found at the periphery of the lung, perhaps in a prior scar, and shows a sheet of larger cells with lacey cytoplasm often within a glandular pattern.
- Small cell carcinoma of the lung is often found centrally in the lung and has cells that have a very high nuclear to cytoplasmic ratio and hyperchromatic with granular chromatin, and the cells often mold against one another.
- Cigarette smoke is well associated with lung cancer risk and contains multiple procarcinogens which can be converted to carcinogens via the P-450 monooxygenase system. Some patients with P-450 system polymorphisms have an even greater propensity to activate these cigarette smoke procarcinogens to carcinogens.

Authors' Note

The opinions expressed herein are those of the authors and are not necessarily representative of those of the Uniformed Services University of the Health Sciences (USUHS), the Department of Defense (DOD), or the United States Army, Navy, or Air Force.

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Subarachnoid Hemorrhage Related to Ruptured Berry Aneurysm

Sarah Meyers, MD[1]

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, diagnostic medicine, therapeutic pathology, central nervous system, berry aneurysm, death certificate, death investigation, intracranial hemorrhage, subarachnoid hemorrhage

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Primary Objective

Objective NSC7.3: Cranial Hemorrhage. Compare and contrast the etiologies and clinical presentations of epidural, subdural, subarachnoid, basal ganglionic, and lobar hemorrhages.

Competency 2: Organ System Pathology; Topic NSC: Nervous System–Central Nervous System; Learning Goal 7: Ischemia of the Brain.

Secondary Objective

Objective AU2.2: Components of the Death Certificate. Discuss the key components of the death certificate; differences among immediate, intermediate, and underlying (proximate) cause of death based on disease process; and the role of mechanisms of death on a death certificate.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic AU: Autopsy; Learning Goal 2: Death Certificate.

Clinical Case

A 47-year-old female with a medical history of migraine headaches, with migraine pain controlled by codeine, is found dead on the floor of her secured residence. No outward signs of trauma or foul play were identified at the scene of death. Given her relatively young age and minimal medical history, an autopsy was requested and performed by the county medical examiner. Following resection of the skull and dura, the following intracranial finding was identified (Figure 1). The pathologist reports that this collection cannot be wiped from the surface of the brain. The hemorrhage appeared to be concentrated at the base of the brain. The circle of Willis was dissected and showed the abnormality identified by the arrow (Figure 2).

Questions/Discussion Points

Given the photograph and the description, what is the name of the finding featured in Figure 1? How would the gross description be different for other types of intracranial hemorrhage? If a CT was performed for this entity, how might the findings be reported?

The photograph shows subarachnoid hemorrhage. A subarachnoid hemorrhage is confined by the arachnoid layer and

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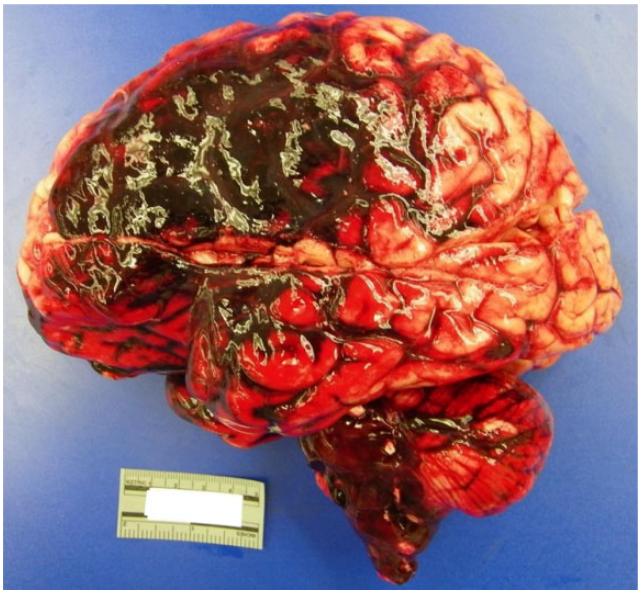

Figure 1. Brain with subarachnoid hemorrhage.

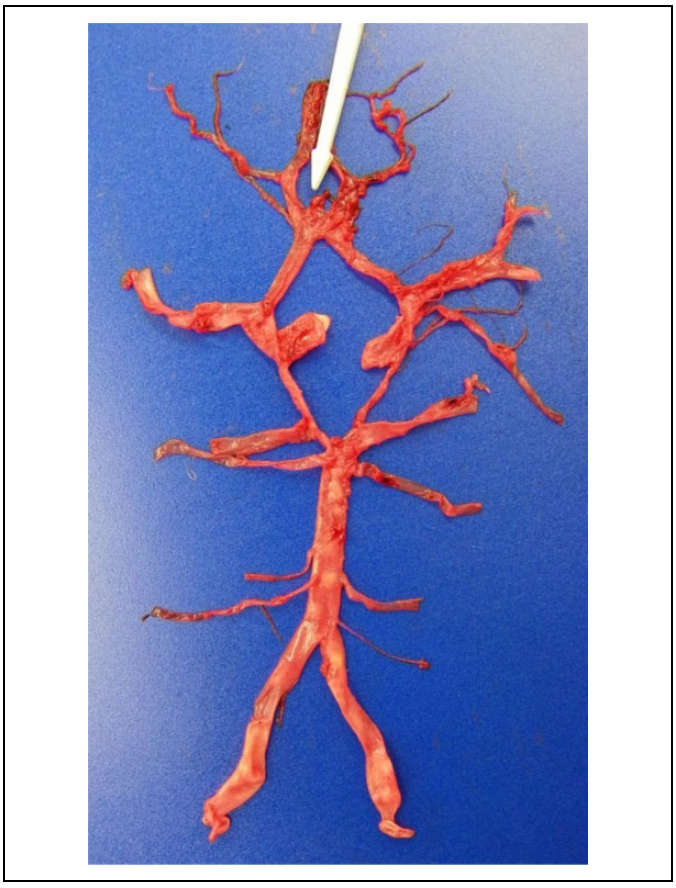

Figure 2. Dissected circle of Willis demonstrating ruptured berry aneurysm at the bifurcation of the anterior communicating artery and the anterior cerebral artery.

cannot be wiped or rinsed away from the brain. Radiographically, subarachnoid hemorrhage would be demonstrated by thin layers of blood overlying structures, such as the sylvian fissure, intrahemispheric fissure, or basal cisterns. Subdural hemorrhage consists of blood filling the potential space beneath the dura, but outside the subarachnoid space. At gross inspection, subdural blood would be able to be wiped or washed away from the surface of the brain and not retained within the cell layer of the subarachnoid space. CT imaging generally shows a crescentic shaped area of hemorrhage outside the brain parenchyma, beneath the skull. Intraparenchymal hemorrhages, such as those related to hypertension or tumors, would be centered within and usually surrounded by brain parenchyma; however, these areas of hemorrhage may expand to communicate with the subarachnoid, subdural, or intraventricular space. CT imaging of intraparenchymal hemorrhage demonstrates blood within the brain itself.

What is the differential diagnosis for the etiology of the finding demonstrated in Figure 1?

Ruptured berry (saccular) aneurysm, trauma, ruptured arteriovenous malformation, extension of intraparenchymal hemorrhage, hematologic disorders, and coagulopathies.[1] Of these entities, the most common cause of clinically significant subarachnoid hemorrhage is due to a ruptured berry aneurysm.[1]

What is the cause of the hemorrhage based on the finding in Figure 2?

Ruptured berry (saccular) aneurysm.

What are the major complications associated with these autopsy findings?

Statistics vary, but up to 50% of patients die within 1 month of an intracerebral aneurysmal rupture and hemorrhage.[1] Similar to this patient, at least 10% of patients die prior to hospitalization for the first bleed.[1] If a patient survives, major morbidity manifests as delayed ischemic complications related to vasospasm, rebleeding, seizures, hydrocephalus, and hyponatremia.[1]

Acting as the medical examiner, please list the cause (immediate and underlying) and manner of death.

The cause of death is the injury or disease process that resulted in a patient's death. Manner of death is defined by public health parameters and is a selection of natural, accident, suicide, homicide, or undetermined. A death certificate should tell the whole story of a patient's history and should work backward from the underlying cause of death to the immediate cause of death. Care should be taken to ensure that the death certificate is specific, concise, and avoids nonspecific mechanisms of death that are universal to all deaths, such as the phrase cardiorespiratory arrest. As such, the first disease process that

occurred in this patient's case was the rupture of the berry aneurysm leading to the subarachnoid hemorrhage. Both of these processes are natural diseases; therefore, the death certificate should be completed as follows:

Cause of death: Subarachnoid hemorrhage (immediate cause)
Due To: Ruptured berry aneurysm (underlying cause)
Manner of Death: Natural

Teaching Points

- Subarachnoid hemorrhage is demonstrated grossly by a layer of blood confined within the subarachnoid space.
- The differential diagnosis for subarachnoid hemorrhage includes a ruptured berry aneurysm, trauma, ruptured arteriovenous malformation, extension of intraparenchymal hemorrhage, hematologic disorders, and coagulopathies.
- Ruptured berry aneurysms have high morbidity and mortality related to short- and long-term complications related to subarachnoid hemorrhage.
- In completing a death certificate, the cause of death should be ascribed to the underlying disease or injury that set the sequence of events in motion to result in the immediate cause of death.

Declaration of Conflicting Interests

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Genetic Mutations and Multifactorial Inheritance: Dilated Cardiomyopathy

Eric S. Suarez, MD[1] and Barbara E. C. Knollmann-Ritschel, MD[1]

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, genetic mechanisms, developmental and functional abnormalities, mutations, cardiovascular, cardiomyopathy, dilated cardiomyopathy, disease mechanisms, genetic diseases, inherited diseases

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Primary Objective

Objective GM1.1: Types of Mutations. Describe different types of mutations that can occur in human disease, and discuss how each of these can produce abnormalities in DNA transcription and/or alterations in the type or amount of protein produced.

Competency 1: Disease Mechanisms and Processes; Topic GM: Genetic Mechanisms; Learning Goal 1: Genetic Mechanisms of Developmental and Functional Abnormalities.

Secondary Objectives

Objective GM1.5: Multifactorial Inheritance and Environmental Factors. Discuss and give examples of disorders associated with multifactorial inheritance and describe how environmental factors can interact with genetic factors to produce or modulate disease.

Competency 1: Disease Mechanisms and Processes; Topic GM: Genetic Mechanisms; Learning Goal 1: Genetic Mechanisms of Developmental and Functional Abnormalities.

Objective CH1.2: Cardiomyopathy. Compare and contrast the clinicopathologic features of dilated, restrictive, and hypertrophic cardiomyopathies.

Competency 2: Organ System Pathology; Topic CH: Cardiovascular—Heart; Learning Goal 1: Heart Failure

Patient Presentation

A 26-year-old male presents to the emergency department with complaints of a 5-month history of progressive dyspnea that became more severe over the past 6 days and prompts this evaluation. Medical history is significant for at least 6 upper respiratory infections over the past 2 years. Family history is significant for 4 cardiac-related deaths in ages between 24 and 38 years involving the 3 last generations of his family, as well as a 29-year-old paternal cousin with heart failure. There is no significant history of alcohol ingestion, toxin exposures, or illicit drug abuse. Physical examination discloses bilateral

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basal lung rales, displaced apical impulse to the left, systolic apical murmur, hepatomegaly of 6 cm below the right midclavicular line, and bilateral low extremity pitting edema extending to 5 cm above the ankles. Recorded vital signs are blood pressure = 105/65 mm Hg, Respiratory Rate = 28 per minute, Heart Rate = 138 per minute, and temperature = 98.9°F.

Diagnostic Findings

Echocardiogram shows marked cardiac enlargement, dilation of all chambers, 35% left ventricle ejection fraction, and left ventricle thrombi. Imaging studies show normal cardiac valves and patent coronary arteries. Laboratory studies reveal moderate B-natriuretic peptide elevations and mild troponin and liver enzyme elevations.

Questions/Discussion Points

What is Your Preliminary Diagnosis and Its Differential?

Dilated cardiomyopathy is the primary diagnosis, based on the clinical findings consistent with heart failure, cardiac enlargement of all chambers, imaging studies showing normal valves and patent coronaries, and functional studies describing decreased ejection fraction. The differential diagnosis based on the clinical findings includes other types of cardiomyopathy such as restrictive or hypertrophic, as well as multiple diseases included within the syndrome of dilated cardiomyopathy per se. Dilated cardiomyopathy can be further categorized as familial and inherited or as acquired. Acquired etiologies include myocarditis; toxins such as cocaine, amphetamines, or heavy metals; autoimmune; endocrine diseases such as hypothyroidism or hyperthyroidism; thiamine deficiency; and ischemic heart disease.[1,2]

What Clinical Considerations Should Follow a Diagnosis of Cardiomyopathy?

When suspecting a cardiomyopathy, the initial considerations are morphologic and functional, which help classify them as dilated, restrictive, hypertrophic, or one of the more unusual types of cardiomyopathy such as right ventricle arrhythmogenic or left ventricle noncompaction cardiomyopathy. Occasionally, these features may overlap or may not be fully developed, such as when you evaluate inherited genetic diseases early in their development.

The extent of organ involvement should be recorded. The manifestations may be limited to only the heart, but the disorder may affect other organs as well, such as skeletal muscle, kidneys or liver as part of the disease process, or may it affect other organs secondarily.

Constructing a pedigree tree may be very useful in determining the inheritance pattern. When evaluating the pedigree, it is possible that the information may be unknown or not investigated at the time of initial presentation. Genetics/familial considerations include autosomal dominant or recessive, X-linked, mitochondrial, or sporadic inheritance patterns which can easily be determined with the family history evaluation.[3]

Etiology of the cardiomyopathy should be investigated. This may include genetic, viral following a myocarditis, autoimmune, toxic, or unknown causes of cardiomyopathy.

The stage of heart failure at the time of presentation should be recorded using criteria of the American Heart Association or New York Heart Association.

What Pathophysiologic Mechanisms Are Involved in the Development of Dilated Cardiomyopathy?

Defects of force transmission, force generation, or calcium handling result in systolic dysfunction, cell death, and fibrosis, producing the dilated cardiomyopathy phenotype. Mutations involving δ-sarcoglycan may cause defects of force transmission; in a similar fashion, defects of force generation may be caused by mutations encoding for sarcomere proteins such as β-myosin.[4] Even in nonfamilial cases of cardiomyopathy, inherited genetic susceptibilities may determine how the cardiac muscle responds to environmental factors such as alcohol or viral myocarditis.

What Are the Inheritance Patterns of Dilated Cardiomyopathy? Can You Give Some Examples?

Approximately 30% to 48% of dilated cardiomyopathies are inherited or familial. Most of the inherited cases are autosomal dominant; but autosomal recessive and X-linked patterns have also been reported. Causative genes predominantly encode for sarcomere (ie, titin [TTN], actin, myosin, troponin) or cytoskeletal (ie, dystrophin, desmin, lamin) proteins. Dystrophin is the same protein involved in the X-linked Duchenne or Becker muscular dystrophies. Less commonly, an X-linked inheritance pattern may be identified in newborns and children as part of the Barth syndrome, which is caused by mutations of the gene tafazzin, which codes for an acyltransferase. Twenty percent of autosomal dominant, dilated cardiomyopathies identified genetically affect genes coding for TTN, a protein that provides structure, flexibility, stability, and chemical signals to the sarcomere.[5] These mutations result in an abnormally short TTN protein.[6] About 8% of all genetic dilated cardiomyopathy cases are caused by deletions or sequence variations of the LMNA gene that, when mutated or deleted, encode for an absent or abnormal lamin A/C protein. Most of these cases also have an associated atrioventricular block clinically, and in this circumstance, implantation of intracardiac defibrillator may be a consideration. Rare autosomal recessive cases result from mutations encoding for troponin I.

How Should You Proceed With the Genetic Evaluation of This Case?

Perform a careful pedigree analysis of all possible affected family members taking into consideration and annotating all possible involved cardiac and extracardiac clinical features. Inherited cardiomyopathies are phenotypically variable in regard to the age of presentation, expressivity, or disease

progression. Mixed forms that do not fit into a single traditional category have been described as several instances of dilated cardiomyopathy have been associated with an arrhythmogenic phenotype. Incomplete penetrance and variable expressivity warrant a high index of suspicion, particularly for first-degree relatives. You may consider genetic testing for first-degree family members, with the caveat that the yield may be much lower than in the cases of hypertrophic cardiomyopathy. The sensitivity of genetic sequencing panels for familial dilated cardiomyopathy cases is 25% but rises up to 40% if the cardiomyopathy coexists with conduction defects. A truncated TTN protein caused by TTN frameshift, nonsense, or splice mutations have been reported in approximately 25% of familial dilated cardiomyopathy cases. Titin encompasses 363 exons with an established role in muscle assembly and function. At present, there seems to be no clear correlation between genotype and phenotype probably because this large gene can undergo extensive alternative splicing. These splicing variants beg for a more refined interpretation of genetic findings.[7] Truncating mutations have also been associated with sporadic cases, suggesting increased susceptibility to environmental effects. The significance of genetic variations is unknown in many instances. Frequently, a genotype–phenotype correlation will be of limited clinical utility in the treatment of the patient, but some instances warrant genetic characterization.

Teaching Points

- Clinical evaluation including complete pedigree analysis is essential in the evaluation of genetic disorders such as dilated cardiomyopathy.
- Penetrance and expressivity are important considerations, especially when evaluating first-degree relatives.
- A truncated protein that fails to transmit or generate force within or across the sarcomere or adequately handle calcium can result from frameshift, nonsense, or splice mutations.
- The clinical significance of mutations is frequently unknown.
- Many dilated cardiomyopathy cases are familial; most commonly autosomal dominant disorders, but autosomal recessive and X-linked inheritance patterns can also be observed.
- Dilated cardiomyopathy clinical presents with heart failure and cardiac enlargement; imaging studies showing normal valves and patent coronaries and a decreased ejection fraction.

Authors' Note

The opinions expressed herein are those of the authors and are not necessarily representative of those of the Uniformed Services University of the Health Sciences (USUHS), the Department of Defense (DOD), or the United States Army, Navy, or Air Force.

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Benign Papilloma of the Breast

Moshe Sadofsky, MD, PhD[1]

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, disease mechanisms, organ system pathology, basement membrane, benign, breast, neoplasia, papilloma

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Primary Objective

Objective N2.1: Prevalence and Geographic Impact on Neoplasia. Describe the prevalence of neoplastic diseases and discuss the environmental factors that influence patients as they move between geographical regions.

Competency 1: Disease Mechanisms and Processes; Topic N: Neoplasia; Learning Goal 2: Environmental Influences on Neoplasia.

Secondary Objectives

Objective N2.2: Mechanisms of DNA Damage Repair. Describe the mechanisms by which exposure to radiation, tobacco, alcohol, or other environmental chemical agents can produce cancer.

Competency 1: Disease Mechanisms and Processes; Topic N: Neoplasia; Learning Goal 2: Environmental Influences on Neoplasia.

Objectives N3.1 through N3.5. Learning Goal 3: Characteristics of Neoplasia. Apply knowledge of the characteristics of neoplasia to discuss the morphologic appearance, classification, biological behavior, and staging of neoplasms.

Competency 1: Disease Mechanisms and Processes; Topic N: Neoplasia.

Objective BR1.1: Clinical Presentation of Breast Lesions. Identify the most frequently diagnosed breast lesions by age of the patient, based on the most common clinical presentations in males versus females.

Competency 2: Organ System Pathology; Topic BR: Breast; Learning Goal 1: Nonneoplastic Disorders of the Breast.

Objective BR1.4: Fibrocystic Change. Discuss the clinical significance of proliferative and nonproliferative fibrocystic change, with and without atypia, and describe how each of these changes and the family history affects the subsequent risk of developing breast cancer.

Competency 2: Organ System Pathology; Topic BR: Breast; Learning Goal 1: Nonneoplastic Disorders of the Breast.

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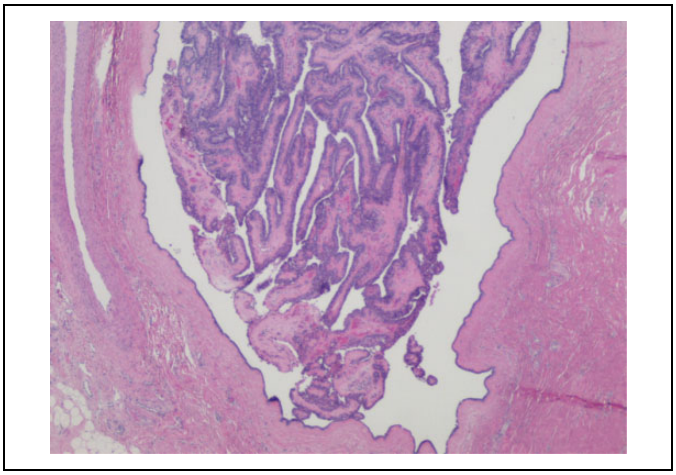

Figure 1. Low-power H&E image from core biopsy of breast.

Patient Presentation

A 37-year-old woman presents to her physician with a palpable density in her left breast. She noticed it 1 month ago and it hasn't changed in size. Her medical history is unremarkable. Medications include oral contraceptives. On examination, she appears somewhat anxious. Her vital signs are within normal limits. Physical examination is remarkable for an ill-defined area of firmness in the left breast in the upper outer quadrant adjacent to the nipple. The region is not tender, and there is no inflammation or discharge. A breast ultrasound core biopsy is obtained.

Questions/Discussion Points, Part 1

Before jumping to the histologic sections, it is worth discussing the differential diagnosis based on the patient presentation.

What is the differential diagnosis of a palpable breast mass?

Our thinking is guided by the history. Is there pain? If so, is it within the breast or associated with the chest wall? Does it change with the hormonal cycle? Is there nipple discharge, and if so, what is its character? These distinctions help determine the likelihood of a true neoplasm of breast origin versus other physiologic possibilities. A thorough discussion is available in the study by Santen. Most importantly, 90% of new nodules presenting in premenopausal women are benign. In younger women, these are usually fibroadenomas, while "in the later reproductive period, hyperplasia, cysts, and carcinoma in situ are more common".[1] As occurs elsewhere in the body, growths may also originate in nonglandular tissues including lipoma, fat necrosis (with a history of injury), and hemangioma. Imaging might suggest an area of increased density within the breast, not explained as simple cyst.

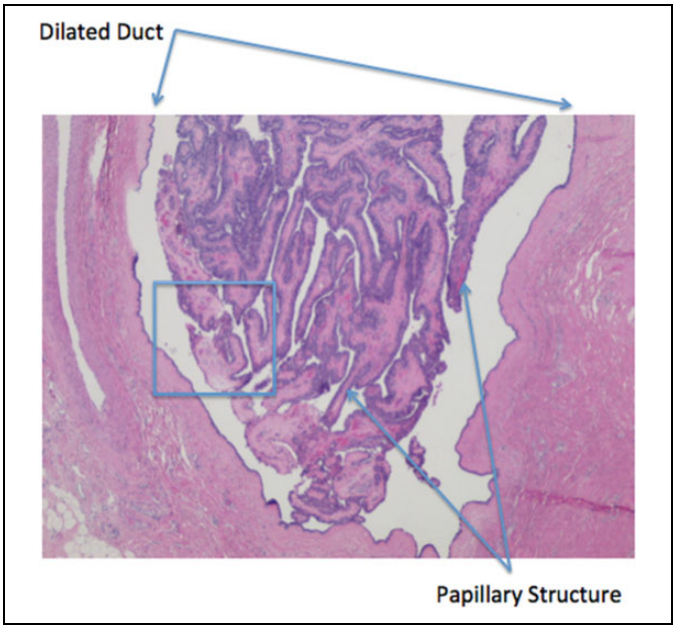

Figure 2. The image of Figure 1 is labeled showing the central papillary structure. A box encloses the region magnified below.

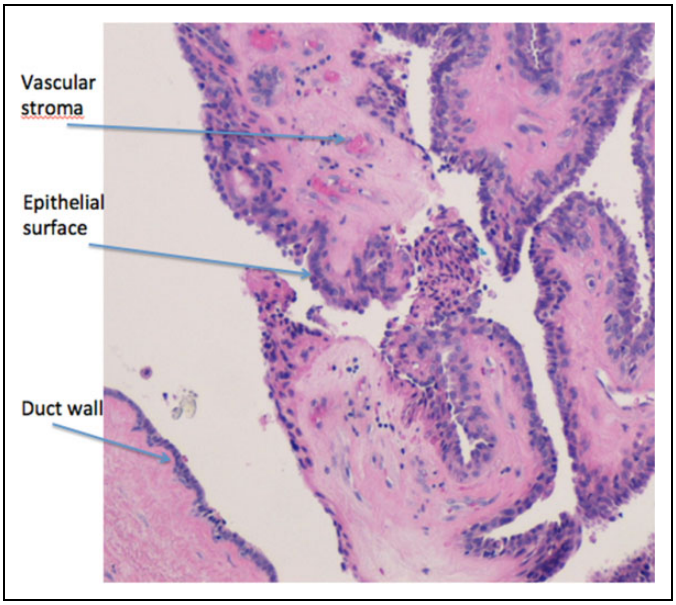

Figure 3. The comparison of the epithelial surface of the central fronds shows a monolayer of basophilic cells similar in appearance to the ductal lining and a fibrovascular eosinophilic stroma.

The biopsy was obtained (Figure 1). Describe the histologic features of this lesion. What is your diagnosis and what is its biologic behavior?

The low-powered Hematoxylin and Eosin (H&E)-stained slide obtained from the biopsy contains the field in Figure 1. Within a large dilated duct sits a structure folded into papillary fronds lined by a basophilic epithelium surrounding

a pink central fibrovascular stroma. These features are labeled in Figure 2.

A box in Figure 2 is seen at higher magnification in Figure 3. Figure 3 shows the duct wall and the epithelial surface of the papillary fronds to be composed of similar cells, forming a simple layer resting upon a basement membrane. The latter is not easy to see directly with these dyes but can be visually enhanced with special stains. Both tissues have matured in the manner characteristic for ductal tissue, with a polarized surface facing the duct lumen. The fronds also contain a stroma and small blood vessels. The structure is named an "intraductal papilloma."

What Does the Name Tell You?

This is a benign proliferation in some ways analogous to adenomas that may occur elsewhere. If it had been malignant, the name would have included the word "carcinoma." Papillomas have 2 main clinical presentations including solitary lesions near the nipple or multiple peripheral papillomas. The latter have a higher rate of atypia or malignancy arising in them. The most important observation is that there is no evidence of invasion. In other words, the epithelium does not penetrate the basement membrane and spread into adjacent areas. This proliferative neoplastic process can be associated with an increased risk of cancer in the future, especially if there is atypical piling up of the epithelial cells on each other (not seen here). In the absence of invasion, this lesion is benign and does not need further treatment. However, the patient should remain alert for changes in the future.

An additional important feature worth remembering is that neoplasia (new growth) includes benign lesions. These may grow to large size and can even become life threatening if they interfere with a function (eg, benign meningioma). Benign doesn't mean, "you can live with it." It means "not invasive."

Other Manifestations of Benign Breast Disorders

Most important, benign lesions of the breast are much more common than malignancies. The incidence of these disorders changes with the age of the patient. An online review of Benign Breast Disease in Women is referenced.[1]

Benign lesions of the breast are often classified in terms of their potential contribution to future breast cancer. In this light, there are 3 common categories:

- Nonproliferative changes (with little to no increased risk of cancer). This includes fibrocystic change and cysts;
- Proliferative lesions without atypia, including this case;
- Proliferative lesions with atypia.

Proliferative disease is associated with a 1.5- to 2-fold increased risk, while proliferative disease with atypia confers a 4- to 5-fold increased risk.[2]

What is the structure and function of the basement membrane that separates the epithelium from the fibrovascular core?

It is widely recognized that all epithelia organize themselves on a structure called the basement membrane. However, the relationship of the cell to this structure is much more interesting and active than many appreciate. Studies reveal "common functions that include the induction and maintenance of cell polarity, the establishment of barriers between tissue compartments, the organization of cells into tissues, and the protection of adherent cells from detachment-induced cell death, anoikis."[3] Although the term membrane is used, it is not a lipid membrane as the term is used elsewhere. Rather, the basement membrane is a complex type of extracellular matrix with an elaborate organization that includes collagen IV, laminins, other connective proteins and heparin sulfate containing proteoglycans. The absolute identity of the components of the basement membrane varies among cell types and are essential for the growth and maintenance of all epithelia.

Teaching Points

A quick review of the normal histology of ductal tissue in the breast shows a simple monolayer of epithelial cells with an underlying basement membrane.

- Despite the proliferative classification of this papilloma, the basement membrane is not violated, so there is no invasion.
- Invasion is an essential hallmark of epithelial malignancy.

Benign lesions of the breast, depending on their microscopic properties, may range in future risk of developing cancer from none at all, to a 4- to 5-fold increase.

Acknowledgment

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Competency 3: Diagnostic Medicine and Therapeutic Pathology

Educational Case Background & Submission Instructions

Background

Becoming a competent physician requires the ability to gain a broad foundation of knowledge, skills, and attitudes essential for independent medical practice. Essential in this is the understanding of the normal and pathological processes of each organ system, the ability to apply disease mechanisms to describe the pathobiology, and the ability to continually improve the diagnostic acumen and optimal treatment decisions through lifelong learning.

The Pathology Competencies for Medical Education (PCME) have detailed learning objectives under each goal that direct medical students and course directors to important facets of each learning goal that can be individually applied by learners. The competencies are divided into three sections—disease mechanisms and processes, organ system pathology, and diagnostic medicine and therapeutic pathology—and allow flexibility for each medical school and learner to apply the learning goals and objectives in a way that can keep the unique design of each curriculum or learning plan. The competencies are purposefully kept broad as they represent the minimum requirements of what pathology course directors across the nation have agreed upon to prepare medical students for entry into any residency program and for the subsequent contemporary practice of medicine.

Educational Cases for the PCME are current, peer-reviewed, and highlight the pathology competencies through fictional (but realistic) learning cases that can easily be adapted to multiple types of educational modalities. Educational Cases reference at least one primary learning objective, but may have one or more secondary learning objective(s). The pathology competencies and learning objectives are clearly indicated in the beginning of each case so that the focus of the educational case is evident. Key elements of the current format include clinical presentation, discussion questions or points, learning points, and references. The clinical presentation may include images or laboratory data for the patient's presentation. The discussion questions or points are questions or statements that promote clinical reasoning followed by detailed explanations of the pathology, medicine, or therapeutics brought up in the discussion point or question. The learning points at the end of the case highlight the main teaching points from the preceding discussion. Thus, the cases demonstrate the application of medical reasoning to clinical scenarios that allow the learner to understand and apply diagnostic principles, incorporating morphologic findings and laboratory values with discussion of the laboratory medicine essentials for accurate diagnosis and treatment. References are included in each case and will allow the reader to review the original sources used to create the learning case or gain additional in-depth information. Thus, the Educational Cases are written in a style that can be easily used or adapted to multiple educational formats, such as small group discussions or flipped classrooms.

Case Submission Guidelines

- Submission Portal: https://mc.manuscriptcentral.com/apc
- Manuscript Type: *Educational Case*
- Key Words:
  - *list "pathology competencies" as first keyword*
  - *list relevant competency, topic, learning goal, and objective keywords, e.g. "disease mechanisms, genetic mechanisms, inheritance patterns"*
  - *other relevant keywords from the case content, e.g. "cystic fibrosis"*
- Abstract: *"None needed"*
- Case Content:
  - Primary (and secondary if applicable) learning objective(s), cited from the PCME (doi: 10.1177/2374289517715040)
    - Example of primary objective formatting:
      Objective GM1.2: Inheritance Patterns. Compare and contrast the inheritance patterns of different types of Mendelian disorders and give examples of each type of pattern.
      Competency 1: Disease Mechanisms and Processes; Topic GM: Genetic Mechanisms; Learning Goal 1: Genetic Mechanisms of Developmental and Functional Abnormalities.
  - Patient Presentation: *Include presentation (History of present illness, past medical history, etc. and physical examination)*
  - Diagnostic Findings: *This can include laboratory findings or histology.*
  - Questions/Discussion Points: *The questions and discussion points should be presented in a logical order to promote clinical reasoning. In addition, you can include additional laboratory data/histologic images in later discussion points. The discussions should thoroughly explain the learning objectives to which the case is applied.*
  - Teaching Points: *These should be covered in your discussion.*
  - References: *Linked to the discussion.*
- Images (if applicable): *All images must be original work or have appropriate approval for publication.*

Accepted Cases

Published Educational Cases receive the same scholarly recognition, citation and merit as other articles published in *Academic Pathology*. Cases accepted for publication will incur an Open Access article processing fee of $500.00 for authors who are faculty and students of APC member departments; $750 for non-members. For more information, contact *Academic Pathology* at journal@apcprods.org or 302-660-4940.

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Educational Case: Infectious Diseases: Pathogenesis, Diagnosis, Treatment, and Prevention

Sheila E. Segura, MD[1], Gloria Ramos-Rivera, MD[1], and Mark Suhrland, MD[1]

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, diagnostic medicine, cytopathology, cytologic diagnosis, infectious diseases, cervix disease, herpes infection, trichomoniasis, candidiasis

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Primary Objective

Objective CYP1.3: Identifying Infectious Diseases. Describe the uses and limitations of cytology, with examples, in identifying common infectious diseases.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic CYP: Cytopathology; Learning Goal 1: Cytologic diagnosis.

Patient Presentation #1

A 32-year-old female, gravida 1 para 0, at 36 weeks of gestation, presented to the OB/GYN clinic complaining of itchiness and pain in the genital area. The patient denied a significant past medical history. Physical examination revealed several small vesicles in the vulvar and vaginal area. A cervical vaginal cytology (PAP) test was performed.

Diagnostic Cytologic Findings, Part 1

Microscopic examination of the SurePath Pap test showed cells with dense, intranuclear inclusions surrounded by a clear halo and multinucleated cells with nuclear molding and chromatin margination beneath the nuclear membrane imparting a clearing or "stained glass appearance" of the nuclei (Figure 1).

What Is Your Differential Diagnosis Based on the Clinical History and Cytologic Findings?

The differential diagnosis for large multinucleated cells on cervical Pap test includes reactive endocervical cells, herpes simplex virus (HSV) infection, syncytiotrophoblasts, low-grade squamous intraepithelial cells, neoplastic cells (such as carcinosarcoma, choriocarcinoma), and radiation- or chemotherapy-induced changes. Based on the cytological features,[1] the final diagnosis for this Pap was "cellular changes consistent with HSV infection."

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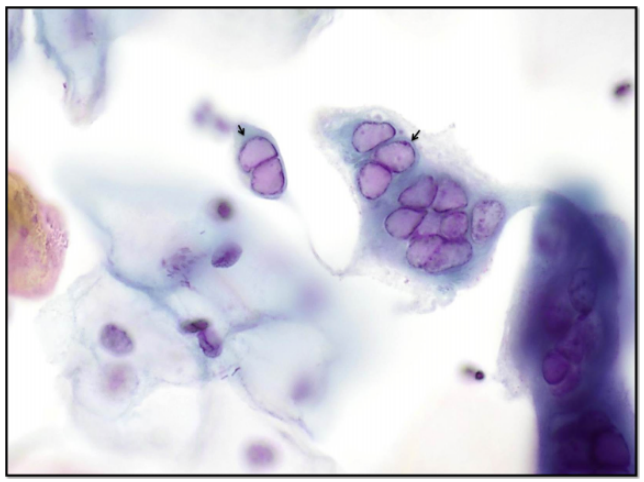

Figure 1. Slide shows a single and a multinucleated squamous cells with nuclear molding and chromatin margination (arrow) beneath the nuclear membrane imparting a clearing or "ground glass appearance" of the nuclei (PAP-stained, high power ×60 magnification).

Questions/Discussion Points, Part 1

What Is Genital Herpes Simplex Virus Infection?

Herpes simplex virus, commonly known as herpes, is a chronic, common, life-long viral infection caused by the 2 members of the herpesvirus family, *Herpesviridae*. Herpes simplex virus are categorized into 2 types: HSV-1 and HSV-2. Herpes simplex virus type 1 is mainly transmitted by oral-to-oral contact and causes infection in or around the mouth (oral herpes). Herpes simplex virus type 2 is almost exclusively sexually transmitted causing infection in the genital or anal area (genital herpes). Most cases of recurrent genital herpes are caused by HSV-2, and approximately 50 million people in the United States are infected with this type of genital herpes.[2,3]

Describe the Symptoms and Transmission of Genital Herpes Simplex Virus

Genital herpes infections often are asymptomatic or might present with mild symptoms that sometimes go unrecognized. Most infected people are unaware that they have the infection. When symptoms do occur, genital herpes is characterized by one or more genital or anal blisters or open sores (also called ulcers), pain during urination, and itching. In addition to genital ulcers, symptoms of recently acquired genital herpes infections often include fever, fatigue, body aches, and swollen lymph nodes. After an initial genital herpes infection with HSV-2, recurrent symptoms are common but often less severe than the first outbreak, and the frequency of outbreaks tends to decrease over time.

Herpes simplex virus type 1 and 2 are transmitted by contact with an infected person. Herpes simplex virus type 2 is mainly transmitted during sex, through contact with genital surfaces, skin, sores, or fluids. Herpes simplex virus type 2 is periodically shed in the human genital tract, and most sexual transmissions occur during periods of asymptomatic shedding. The majority of HSV-1 infections spread easily via contact with sores, saliva, and surfaces in or around the mouth causing oral herpes infection. However, HSV-1 can also be transmitted to the genital area through oral–genital contact to cause genital herpes.[3]

Both viruses may also be transmitted vertically during childbirth. However, the risk of infection transmission is minimal if the mother has no symptoms or exposed blisters during delivery. The risk is considerable when the mother is infected with the virus for the first time during late pregnancy.

How Is Herpes Simplex Virus Infection Diagnosed?

The patient's prognosis and the type of counseling needed depend on the type of genital herpes (HSV-1 or HSV-2) causing the infection; therefore, the clinical diagnosis of genital herpes should be confirmed by type-specific laboratory testing. Both type-specific virologic and type-specific serologic tests for HSV should be available in clinical settings that provide care to persons with or at risk for sexually transmitted diseases (STDs).[2] The Centers for Disease Control and Prevention recommends that persons with genital herpes should be tested for HIV infection as well.[2]

The following tests are used for HSV diagnosis:

- *Viral culture.* This test involves taking a tissue sample or scraping of the sores for examination in the laboratory. The sensitivity of viral culture is low, especially for recurrent lesions, and declines rapidly as lesions begin to heal.
- *Polymerase chain reaction test.* Polymerase chain reaction is used to copy the DNA from a sample of blood, tissue from a sore, or spinal fluid. The DNA can then be tested to establish the presence of HSV and determine which type of HSV. Polymerase chain reaction is the test of choice for diagnosing HSV infections affecting central nervous system (CNS) and systemic infections.
- *Blood test.* Both type-specific and type-common antibodies to HSV develop during the first several weeks after infection and persist indefinitely. The blood sample is analyzed via enzyme-linked immunosorbent assay which detects IgM and type-specific IgG.

Although the cytologic detection of cellular changes associated with HSV infection is an insensitive and nonspecific method of diagnosing genital lesions (ie, Tzanck preparation), the cytologic changes of infected cells are recognized in PAP cervical smears.

In 1989, the Bethesda System (TBS) was introduced to standardize the reporting cervical cytology PAP results and to incorporate the insights into human papillomavirus (HPV) biology and cervical disease association. The current 2014

TBS, like its predecessors, recommends the use of a specific format for the cytology cervical report.[1]

The cytologic features of the HSV-infected squamous cells are variable. The infected cells can show accumulation of viral particles within the nuclei, resulting in an eosinophilic inclusion, known as Cowdry inclusions, which are classified as type A (inclusion in the nucleus) and type B (inclusion in the cytoplasm), which are seen in cytomegalovirus infection. The cells can also show lysis of the chromatin giving a glassy appearance to the nuclei. The infected cells aggregate forming a **M**ulti-nucleated cell with nuclear **M**olding and chromatin **M**argination (3 M's of herpes) features easily recognized under the microscope[1,4]; however, some other lesions or changes may mimic HSV infection on cytologic examination, including reactive or reparative changes, air drying artifact, multinucleated giant cells, poor cell preservation, radiation effect, among others.[4] Under the current Bethesda system for reporting PAP results, for the cytologic changes caused by HSV infection, it is recommended to interpret it as "cellular changes consistent with HSV.[1]

Which Are the Possible Complications of Herpes Infection?

Severe disease. In immunocompromised people, such as those with advanced HIV infection, HSV-1 can have more severe symptoms and more frequent recurrences. Rarely, HSV-1 infection can also lead to more severe complications such as encephalitis or keratitis (eye infection).

Genital herpes in pregnancy and neonatal herpes. Neonatal herpes can occur when an infant is exposed to HSV in the genital tract during delivery. This is a rare condition, occurring in an estimated 10 out of every 100 000 births globally, and the risk of HSV transmission to the neonate from an infected mother is high (30%-50%) among women who acquire genital herpes near the time of delivery and low (<1%) among women with prenatal histories of recurrent herpes or who acquire genital HSV during the first half of pregnancy.[2] Neonatal HSV infection can be divided into 3 clinical groups: (1) skin, eyes and mouth disease (SEM) is a localized infection affecting the skin, eyes, or mouth; (2) CNS disease is defined as encephalitis with or without SEM disease, and (3) disseminated disease involves infection in multiple organ systems and can include hepatitis, pneumonitis, and disseminated intravascular coagulation. Cutaneous lesions may be seen in all types and disseminated disease may occur with or without the presence of CNS disease.[3]

Prevention of neonatal herpes depends both on preventing acquisition of genital HSV infection during late pregnancy and avoiding exposure of the neonate to herpetic lesions and viral shedding during delivery. Women without symptoms or signs of genital herpes or its prodrome can deliver vaginally. Although cesarean delivery does not completely eliminate the risk for HSV transmission to the neonate, women with recurrent genital herpetic lesions at the onset of labor should deliver by cesarean delivery to reduce the risk for neonatal HSV infection.[2] Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered intravenously to pregnant women with severe HSV infection. All infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir.

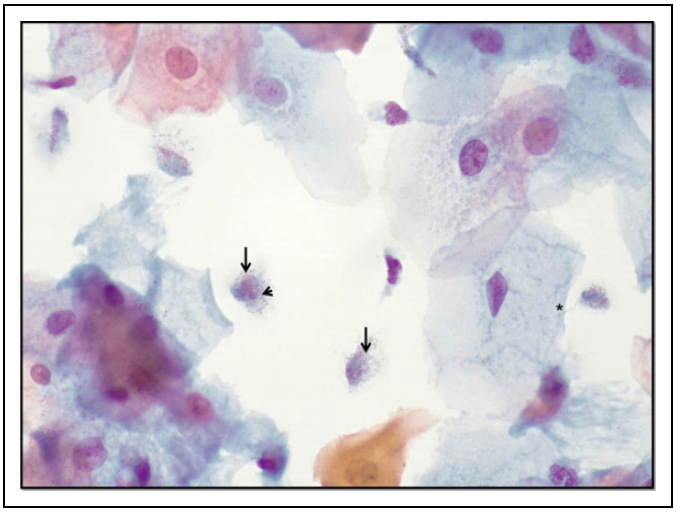

Figure 2. Slide shows several oval-shaped organisms (arrow) with eccentric dark nuclei (arrow head) and gray cytoplasm with red granules. A flagella (asterisk) is also seen. Benign squamous cells are present in the background. These organisms are consistent with *Trichomonas vaginalis* (PAP-stained, high power ×60 magnification).

What Is the Treatment for Herpes Infection?

Antivirals, such as acyclovir, famciclovir, and valacyclovir, are the most effective medications available for people infected with HSV. These can help to reduce the severity and frequency of symptoms, but cannot cure the infection.[2,3]

In our case, the patient was treated with oral acyclovir with improvement of the symptoms. Soon after, she delivered a healthy female baby. Her HIV testing was negative.

Patient Presentation #2

A 67-year-old male with a past medical history of urolithiasis and blood in his urine (gross hematuria) presented to his primary care physician for follow-up. Urine was collected and sent for cytologic examination.

Diagnostic Cytologic Findings, Part 2

Microscopic examination of the slide revealed benign urothelial and squamous cells in a background of acute inflammation and red blood cells. Incidentally, scattered, small, oval-shaped "cells" with eccentric dark nuclei and gray cytoplasm with rare red cytoplasmic granules were also seen (Figure 2).

What Is Your Differential Diagnosis Based on the Clinical History and Cytologic Findings?

The differential diagnosis for these small "cells" includes degenerated inflammatory cells, cellular debris, cellular fragments, and parasites. The cytologic findings were consistent with *Trichomonas* organisms.

Questions/Discussion Points, Part 2

What Is Trichomoniasis and How Is It Transmitted?

Trichomonas vaginalis (commonly known as "trich") is an anaerobic, flagellated protozoan parasite and the causative agent of the STD trichomoniasis. Trichomoniasis is the most prevalent nonviral STD in the United States, affecting an estimated 3.7 million people.[5]

Trichomoniasis is typically found in sexually active patients. Transmission occurs predominantly via sexual intercourse. In women, the most commonly infected part of the body is the lower genital tract (vulva, vagina, cervix, or urethra). In men, the most commonly infected body part is the urethra. It has not been isolated from oral sites, and rectal prevalence appears to be low in men who have sex with men.[5]

What Are the Signs and Symptoms of Trichomoniasis?

About 70% to 85% of infected people have minimal symptoms or are asymptomatic.[5] When trichomoniasis does cause symptoms, they can range from mild irritation to severe inflammation. Some people are symptomatic within 5 to 28 days after infection. Symptoms can come and go, and untreated infections might last for months to years.[5,6]

Some infected men have symptoms of urethritis (urethral discharge) and pain during urination, and some infected women have vaginal discharge that might be diffuse, malodorous, or yellow-green with or without vulvar irritation. Other symptoms includes itching, discomfort during sexual intercourse or urination, and cervicitis in women, which is characterized by purulent discharge and easily induced endocervical bleeding, also known as "strawberry" cervix (due to capillary dilation as a result of the inflammatory response).

What Are the Complications of Trichomoniasis?

Trichomonas vaginalis infection is associated with 2- to 3-fold increased risk for HIV acquisition. It also increases the susceptibility to other viruses, including herpes and HPV. In pregnant women, *T vaginalis* infection has been associated with an increased risk of low birth weight, preterm delivery, and intrauterine infection.[5]

Neonatal trichomoniasis has been described.[6] Respiratory or genital infection in the newborn may also occur. In men, complications of untreated trichomoniasis include prostatitis, epididymitis, urethral stricture disease, and infertility, potentially resulting from decreased sperm motility and viability.

How Is Trichomoniasis Diagnosed?

It is not possible to diagnose trichomoniasis based on symptoms alone. In women, vaginal trichomoniasis has historically been diagnosed by wet mount microscopy, which is performed by placing a small amount of vaginal discharge on a microscope slide and mixing with a few drops of saline solution. The slide is then examined under a microscope at low or medium power and a "corkscrew" motility is observed (parasite moving through the field). It is the most common method for *T vaginalis* diagnosis because of convenience and relatively low cost.[5,6]

Culture was considered the gold standard method for diagnosing *T vaginalis* infection before molecular detection methods became available. *Trichomonas vaginalis* may be accurately identified on Pap smear by morphology alone, but this test yields low sensitivity (50%-80%) and false-positive results are also common with this technique.[5] Cellular debris and degenerated inflammatory cells may be mistaken for trichomonads on cytologic examination.[4]

The use of highly sensitive and specific methods using molecular techniques for detecting antigens, DNA, or RNA are currently recommended for diagnosing *T vaginalis*.[5]

What Is the Treatment for Trichomoniasis?

Trichomoniasis can be treated with nitroimidazole, which is the only class of antimicrobial medications known to be effective against *T vaginalis* infections. Of these drugs, metronidazole and tinidazole have been cleared by the Food and Drug Administration (FDA) for the oral or parenteral treatment of trichomoniasis. It is not recommended to drink alcohol within 24 hours after taking this medication.

Because of the high rate of reinfection among women treated for trichomoniasis ($\sim$17%), retesting for T vaginalis is recommended for all sexually active women within 3 months following initial treatment regardless of whether they believe their sex partners were treated.[5] Concurrent treatment of all sex partners is critical for symptomatic relief, microbiologic cure, and prevention of transmission and reinfections. Current partners should be referred for presumptive therapy to avoid reinfection.

Although metronidazole crosses the placenta, data suggest that it poses a low risk to pregnant women. No evidence of teratogenicity or mutagenic effects in infants has been found in multiple studies of pregnant women. Women can be treated with 2 g metronidazole in a single dose at any stage of pregnancy. The patient and his partner were treated with oral metronidazole.

Patient Presentation #3

An 11-month-old girl with 1-month history of emesis, gagging, and choking with textured foods was brought to her pediatrician by her parents and, after examination, was admitted for management. The prior month, she was briefly admitted to the

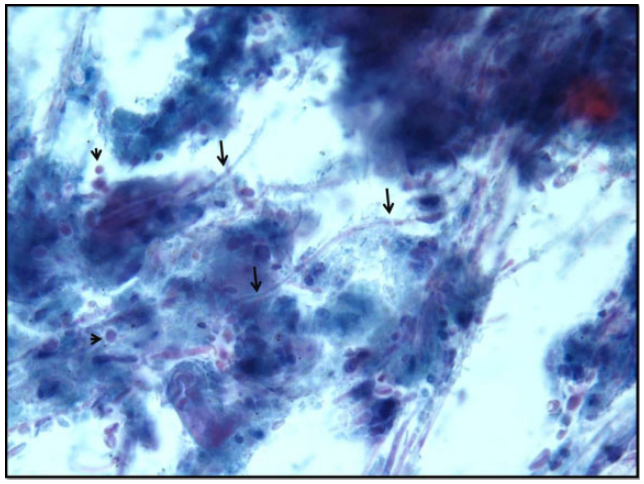

Figure 3. Microscopic examination of the smears reveled esophageal squamous mucosa admixed with acute inflammatory cells and fungal hyphae (arrow) and spores (arrow head), morphologically consistent with *Candida* species (PAP-stained, high power ×60 magnification).

hospital for a respiratory syncytial virus bronchiolitis and was given oral prednisone 10 mg twice a day for 5 days. On current admission, the baby underwent an esophagogastroduodenoscopy. The middle to distal esophagus was covered with yellow-white plaques scattered over the mucosa. The mucosa was hyperemic and friable, and the plaques could not be washed off. The lesions bled easily at the site of attachment, where they were brushed for cytology, Gram stain, and fungal culture. Biopsies were also taken.

Diagnostic Cytologic Findings, Part 3

Microscopic examination of the cytology brushing smears reveled esophageal squamous cells admixed with acute inflammatory cells. Fungal pseudohyphae and spores, morphologically consistent with *Candida* species, were also present (Figure 3). The Grocott-Gomori's methenamine silver (GMS) stain on smears and culture also showed *Candida* organisms. The biopsy results were consistent with chronic esophagitis suggestive of reflux, with *Candida*-like organisms. She was treated with oral fluconazole and omeprazole with improvement of her symptoms.

Questions/Discussion Points, Part 3

What Is Candidiasis?

Candidiasis is a fungal infection caused by the yeast *Candida*. More than 20 types of *Candida* can cause infection, with *Candida albicans* being the most common. *Candida* yeasts are generally present in healthy humans, frequently as part of the human body normal oral and intestinal flora, and particularly on the skin, but it can become pathogenic if the host's luminal flora or immune defenses are altered.[7,8]

Factors that increase the susceptibility of the host to *Candida* infection are various malignancies, immunodeficiency states, diabetes, stress, antibiotic treatments, nutrient deficiency, endocrinopathies, long-term use of steroids, and other immunosuppressive drugs.

What Is the Clinical Presentation of Candidiasis?

Signs and symptoms of candidiasis vary depending on the area affected. Most candidal infections result in minimal complications such as redness, itching, and discomfort, though complications may be severe or even fatal if left untreated in certain populations.

The clinical presentation can be broadly divided into cutaneous candidiasis, mucosal candidiasis, and systemic candidiasis. In immunocompetent persons, candidiasis is usually a localized infection of the skin, fingernails or toenails (onychomycosis), or mucosal membranes. The most common manifestation of candidal infection in infants is diaper dermatitis. Candida organisms can also cause intertrigo in older individuals. The oral infection or oropharyngeal candidiasis, commonly called "thrush," frequently occurs in infants and toddlers. Infection in the esophagus is called esophageal candidiasis or Candida esophagitis, and the most common presenting complaints are difficulty and pain with swallowing, with one-third of patients also having oral thrush. Infection of the vulva or vagina also referred as "yeast infections" or "vulvovaginal candidiasis" affects nearly 75% of women, usually causing mild symptoms, such as itching, burning, soreness, irritation, and a whitish or whitish-gray cottage cheese-like discharge.[7]

Candida organisms can cause severe systemic infections in immunocompromised patients, such as patients with AIDS, premature babies, critically ill patients, or patients with cancer. In these patients, *Candida* yeast enters the bloodstream and spreads to internal organs, such as CNS, kidneys, liver, bones and joints, among others.

How Is Candidiasis Diagnosed?

Depending on the clinical presentation, several diagnostic tests are available and include the following:

- Mucocutaneous candidiasis—Using a wet mount, scrapings or smears obtained from skin, nails, or oral or vaginal mucosa are examined under the microscope; a potassium hydroxide (KOH) smear, GMS stain, or methylene blue is useful for direct demonstration of fungal organisms.
- Cutaneous candidiasis—Using a wet mount, scrapings or smears obtained from skin or nails can be examined under the microscope; KOH smears are also useful.
- Genitourinary candidiasis—A urinalysis and urine fungal cultures are useful. A sample of vaginal discharge can be examined under the microscope or sent to a laboratory for a fungal culture.

- Gastrointestinal candidiasis—Endoscopy with or without biopsy and brushings. Samples are submitted for microscopic examination, GMS stain, and culture.
- Systemic candidiasis—Usually blood cultures.

Candida is a common finding on PAP cervical smears and identification does not necessarily indicate infection (commensal in vaginal mucosa). Noncellular substances such as fibrin and contaminants such as carpet fibers or other fungi can be also mistaken with *Candida* under microscopic examination. The Bethesda system recommends reporting these fungi as "fungal organism morphologically consistent with *Candida spp*".[1]

How Is Candidiasis Treated?

Candidiasis is generally treated with antifungal medications; these include clotrimazole, nystatin, fluconazole, voriconazole, amphotericin B, and echinocandins. The management also depends on the clinical presentation.[7]

- Cutaneous candidiasis—Most localized cutaneous candidiasis infections can be treated with any number of topical antifungal agents.
- Mucocutaneous candidiasis—For oral cases, topical antifungals are used. For severe infections, treatment with oral agents is commonly used.
- Esophageal candidiasis—Treatment requires systemic therapy with fluconazole.
- Systemic candidiasis—Treatment requires systemic intravenous therapy.

Teaching Points

- Some infections are easily recognized with cytologic examination of PAP and other body site specimens.
- Herpes infections, oral and genital, are common chronic infections due to the herpes virus (HSV-1 and HSV-2), characterized by itching and blisters/sores on the mouth and/or genital area.
- Genital HSV in pregnant women can be complicated with neonatal herpes.
- Trichomoniasis, caused by the *T vaginalis* parasite, is one of the most common STD infections in the United States, and is usually asymptomatic.
- *Candida spp* is a fungus (yeast), part of the human body normal mucocutaneous and intestinal flora, but it can become pathogenic if the host's luminal flora or immune defenses are altered.
- Although HSV, *Candida spp* and *Trichomonas* infections can be identified with cytologic examination, false-positive results are common, sometimes requiring alternative confirmatory tests.

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Educational Case: Death Certification and the Role of the Medical Examiner/Coroner

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, diagnostic medicine, autopsy, death certificate, forensic autopsy, reportable deaths, cause of death, manner of death, coroner, medical examiner

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Primary Objective

AU 2.2: Components of the Death Certificate. Discuss the key components of the death certificate; difference among immediate, intermediate, and underlying (proximate) cause of death based on disease process; and the role of mechanisms of death on a death certificate.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic AU: Autopsy; Learning Goal 2: Death Certificate.

Secondary Objective

AU 3.2: Reportable Deaths. Identify circumstances of death that need to be reported to the medical examiner/coroner.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic AU: Autopsy; Learning Goal 3: Forensic Autopsy.

Patient Presentation

A 45-year-old male is admitted to the hospital from his skilled nursing facility 1 month prior to his death, with clinical signs and symptoms of sepsis. Urine and blood cultures confirm the clinical suspicion of urosepsis due to *Escherichia coli*. Medical history includes obesity, quadriplegia, neurogenic bladder with indwelling catheter, autonomic instability, hypertension, obstructive sleep apnea, and diabetes mellitus. The patient develops pneumonia and his oxygenation status worsens 2 days prior to his death. He is intubated and sedated. A lung biopsy is performed and shows changes consistent with diffuse alveolar damage. The clinical team meets with the family for a care conference and shares the results of the biopsy. The clinical team states that, due to his underlying diseases and the severity of his current illnesses, it is not likely that he will survive the current hospitalization. The family decides to transition the patient to comfort care and he dies 2 days after developing acute respiratory distress syndrome.

Diagnostic Findings, Part 1

No additional information is gathered by this medical provider and the death certificate is completed as follows:

- (Immediate) Cause of death: Cardiorespiratory failure
- Due to (intermediate cause of death): *E coli* sepsis
- Manner of death: Natural

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Questions/Discussion Points, Part 1

What is the difference between cause and manner of death?

Cause of death is an injury or disease process that resulted in an individual's death.[1-4] A myriad of terms may be used to describe cause of death, including disease processes such as acute myocardial infarct or injuries such as gunshot wound of the head. When sequences of injuries or events occur, the cause of death portion of the death certificate may be further subclassified into immediate (the last injury or disease process in the sequence or the event immediately before death), intermediate, and underlying cause of death (the injury or disease that set off the sequence of events that resulted in death, also known as the proximate cause of death).[1-4] These terms are connected via "due to" statements on a death certificate. For example, if an individual sustains a myocardial infarct, from arteriosclerotic heart disease, which subsequently ruptures causing cardiac tamponade from hemopericardium, the cause of death would be listed as such:

- Immediate cause of death: Hemopericardium with cardiac tamponade
- Due to: (intermediate cause of death): Ruptured myocardial infarct
- Due to (underlying cause of death/proximate cause of death): Arteriosclerotic heart disease

Manner of death is a public health categorization that generally includes only 5 options: natural (a death due to disease processes), accident (nonnatural injuries caused the death; the majority of traffic collisions and drug toxicity deaths are certified as such), suicide (an individual intentionally acted to end their life), homicide (another individual/s caused injuries that resulted in a death), and undetermined (certified when there is conflicting or insufficient information to categorize).[1-4] It is important to note that manner of death classification is strictly defined by public health terminology and not intended to dictate legal actions (for example, if a 2-year-old finds a gun and shoots another individual, the death may be classified as a homicide, as one individual caused the death of another individual; however, murder or manslaughter charges are not likely to be filed against the 2-year-old. In another example, if a pedestrian is struck by a vehicle and dies as the result of blunt force injuries sustained in that collision, the manner of death may be certified as accident. This does not preclude legal charges, including vehicular manslaughter charges, from being filed against the driver of the vehicle).

Is this death certificate complete? If it is not, please state what should be changed or what additional information may be necessary to complete the death certificate?

The death certificate is not complete. At this time, the physician completing the death certificate does not have enough information. Although the immediate and intermediate causes of death are known (acute respiratory distress syndrome due to *E coli* urosepsis), the clinician should ask themselves why a 45-year-old male developed these conditions to the degree that they caused death. Phrased another way, a healthy 45-year-old male should likely not develop urosepsis, so what is different about this individual patient that caused this disease to develop and cause his death? In this situation, the indwelling catheter is the likely origin for the urosepsis, which was placed due to a neurogenic bladder related to quadriplegia. The cause of the patient's quadriplegia needs to be established, as it may relate to the underlying cause and manner of death. In addition, as specific time intervals are known for the individual elements of the immediate and intermediate causes of death, these time intervals should be listed in the appropriate section of the death certificate.

Should "cardiorespiratory failure" be listed as an immediate cause of death?

Cardiorespiratory failure is most appropriately categorized as a mechanism of death and is the terminal mechanism of death for most individuals. Death certificates not only serve to provide family members with important information about disease processes but are also important resources for public health data collection and monitoring of diseases (such as cancer and heart disease) and injury subtypes. As such, cardiorespiratory failure is too nonspecific to be of assistance to either the family of the decedent or public health departments and should not be included in this death certificate. The background information provided in the clinical history is sufficient to provide a specific cause of death.

Diagnostic Findings, Part 2

The original death certificate is filed and the family elects cremation as final disposition for the body. The funeral director in charge of the cremation calls the local medical examiner's office to inquire if the bullet in the deceased's spine needs to be removed prior to cremation.

Questions/Discussion Points, Part 2

What additional steps should the medical examiner's or coroner's office complete to investigate this death?

The medical examiner's or coroner's office is tasked with investigating unexpected, unexplained, and unattended deaths of individuals in the communities they serve. Reports of deaths are usually made by medical personnel and law enforcement; however, anyone, including family members and funeral directors, may report circumstances of death to the office, as occurred in this case. Given the remote trauma and potential retained evidence (the bullet) available for recovery, the medical examiner's office will usually begin by obtaining law enforcement and medical records to compile information used to complete a death certificate. Depending on circumstances,

the individual may be brought for a postmortem examination to retrieve the projectile. Of note, given that remote trauma was involved in the death, this death would fall under the jurisdiction of the medical examiner or coroner and should have been reported by medical personnel at the time of his death.

In this situation, law enforcement investigation and medical records indicate that the deceased was shot by an unknown assailant 20 years prior to his death, resulting in quadriplegia, neurogenic bladder, and finally urosepsis, which ultimately resulted in his respiratory distress syndrome.

Should the death certificate be changed, and if so, please list the immediate, intermediate, and underlying cause of death and the manner of death?

A death certificate should tell the whole story of this patient's history and therefore should be amended to work backward from the underlying cause of death (the disease or injury that set off the sequence of events that resulted in death) to the immediate cause of death (the last event/injury in the sequence, in this case, acute respiratory distress syndrome). A death certificate should be amended and reissued as the cause of death statements is incomplete and the manner of death is incorrect. As another individual caused the injury that set off the chain of events that resulted in the individual's death, the most appropriate manner of death is homicide. The death certificate, as signed by the medical examiner following autopsy examination and investigation, read as follows:

- Immediate cause of death: Acute respiratory distress syndrome (Time interval: 2 days)
- Due to: *E coli* urosepsis (time interval: 1 month)
- Due to: Quadriplegia with neurogenic bladder (time interval: 20 years)
- Due to: Gunshot wound of the back
- Manner of death: Homicide

Teaching Points

- The cause of death is the disease or injury that resulted in an individual's death and should be categorized from the first disease or injury (the underlying cause of death) that set off the sequence that lead to the immediate cause of death.
- Each death must be traced back to the inciting disease or injury, which may have occurred years prior to the death.
- "Cardiorespiratory failure" is a nonspecific mechanism of death that provides insufficient detail about the circumstances of death and does not allow for important information to be passed to decedent's families or public health monitoring systems. Whenever possible, specific disease processes and injuries should be listed as causes of death for accurate death certification.
- The medical examiner's office or coroner's office are tasked with investigating unexpected, unexplained, or unattended deaths in a particular region. Medical providers are responsible for reporting deaths that may fall under the medical examiner's or coroner's jurisdiction to the appropriate office.

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Educational Case: Wrong Blood in Tube

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, preanalytic error, wrong blood in tube, quality improvement, process control, specimen identification

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Primary Objective

Objective GP1.1: Pre- and Postanalytical Errors. Give examples of common sources of preanalytical and postanalytical errors and categorize errors when the following procedures are not properly followed: pairing patient/specimen identification with the requisition forms, using correct specimen containers/tubes for specific tests, and timing of collection, transport, and storage.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic GP: General Principles; Learning Goal 1: Laboratory Tests.

Patient Presentation

A 35-year-old woman is scheduled for a tubal ligation, and a preoperative type and screen is sent. She had never been transfused at this facility. A type and screen was drawn 6 months ago and showed that she was A positive with a negative antibody screen.

Diagnostic Findings, Part I

Results from the current type and screen revealed the sample was O positive with a negative antibody screen.

Questions/Discussion Points, Part I

What Are the First Steps Taken Upon Sample Receipt?

Check that the sample is labeled with 2 identifiers. AABB publishes standards that are required to ensure the safety of blood products in all steps from donation of blood to testing of blood products to transfusion of blood products. *Standards* specifically indicate that "identifying information for the patient and the sample shall correspond and be confirmed at the time of collection using two independent identifiers."[1,2] Another standard says that "the transfusion service shall confirm that all identifying information on the request is in agreement with that on the sample."[1,2] The purpose of using 2 identifiers is to ensure that the blood sample is from the correct patient, and should that patient need blood products, the correct blood products can then be issued.

Review the patient history

The history review is a required step in sample processing. The standards indicate that "there shall be a process to ensure that the historic records for the following have been reviewed . . . ABO group and Rh type. . . . These records shall be compared to current results, and any discrepancies shall be investigated and appropriate action taken . . . ."[2,3] The purpose of reviewing the historic records is to help ensure that if there is

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an accidental mislabeling of a patient sample, it will be identified before any blood products are administered to the patient.

What Possible Explanations Should Be Considered?

Except in 1 particular circumstance, the blood type of a patient should not change. There are a limited number of possible explanations for the current findings. The current sample could be from the wrong patient. The sample taken 6 months ago could have been from the wrong patient. Or, if the patient had a stem cell transplant in the interval from a type O allogeneic donor, her blood type could have changed.

What Should the First Steps Be to Determine the Etiology of the Problem?

There are 2 very important steps that need to be completed to investigate a possible mislabeling of a blood sample. The first is to get the history to be sure the patient did not have a transplant, and in addition to ask for another sample to be drawn from the patient to see whether it matches the historical data or the data from the current blood sample.

Diagnostic Findings, Part 2

Evaluation reveals that the patient has not had a stem cell transplant. A second sample is sent for evaluation which is determined to be A positive, negative antibody screen.

Questions/Discussion Points, Part 2

What Are Your Conclusions?

The sample drawn earlier that day was from the wrong patient. The phlebotomy area should be alerted as there may be another incorrect sample if this was a single direct switch of identifiers on the tube (another patient who is really an O may have been typed as an A). For patients that are hospitalized, it is just as important to evaluate where the blood sample came from and investigate if there could be an accidental mislabeling of samples.

Diagnostic Findings, Part 3

A second patient was not found.

Questions/Discussion Points, Part 3

What should be done in follow-up of this event?

Follow-up regarding process control, patient identification, and labeling should be done. This should include a review of the training and competency of any involved health-care professionals, which may reveal the need for additional training.

Teaching Points

- Patient identification is critical to patient safety and diagnostic accuracy.
- Possible patient identification errors must be investigated fully and promptly, as more than 1 patient may be involved.

Reducing errors requires strict adherence to clinical procedures. In this example, samples must be labeled with 2 identifiers in the presence of the patient. All identifying information on the request must be in agreement with the sample label.

- The history review is a required step in specimen processing.

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Educational Case: Primary Osteosarcoma

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, musculoskeletal, bone neoplasia, bone, osteosarcoma, primary bone tumors, malignant bone tumors, osteosarcoma risk factors, osteosarcoma staging, tumor staging

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Primary Objective

Objective MS1.2: Bone-Forming Sarcomas in Children: Describe the most common benign and malignant bone-forming tumors in children and adolescents in terms of clinical presentation, radiologic findings, histologic features, treatment, and prognosis.

Competency 2: Organ System Pathology; Topic: Musculoskeletal System (MS); Learning Goal 1: Bone Neoplasia.

Secondary Objective

Objective SP1.4: Staging: Describe the information that the pathologist obtains from a resected tissue specimen, how this information is reported, how it is combined with clinical information to stage the tumor, and how staging information is used to guide treatment.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic: Surgical Pathology (SP); Learning Goal 1: Role in Diagnosis.

Patient Presentation

A 14-year-old male patient presents to the emergency department with severe pain in his right knee. The pain has been intermittent for the past 10 weeks, appearing and disappearing sporadically. The discomfort has grown more regular in the last week and is now compounded by marked swelling around the knee. Further interview reveals that the patient plays on a youth soccer team, and his knee feels especially painful during practice. His parents attributed the symptoms to "growing pains," as the patient's height and weight have been increasing appropriately for his age, and he has had no known skeletal diseases—nor any serious conditions—prior to onset of the pain.

Diagnostic Findings, Part I

Vital signs are evaluated and found to be normal. No systemic symptoms are noted. Physical examination reveals a large, palpable mass on the anterior aspect of the right proximal tibia. The mass is tender to palpation, but not warm to the touch.

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Question/Discussion Points, Part I

Discuss the Differential Based on the Clinical Presentation

The patient's large and painful tibial mass is nonspecific, and the differential diagnosis remains broad. At one level, we may consider whether this mass is neoplastic or non-neoplastic. If non-neoplastic, diagnoses might include Osgood-Schlatter disease, subacute osteomyelitis, or a reactive soft tissue lesion such as myositis ossificans. If the mass were neoplastic, one would first have to decide whether the neoplasm was benign or malignant and whether it involved the bone, soft tissue, or both.

For a patient of this age, the most likely malignancies of the bone are osteosarcoma and Ewing sarcoma. Chondrosarcoma may be considered alongside the two—though in its most common form, chondrosarcoma typically presents in the axial skeleton of persons above 40 years old. The mass may be a metastatic tumor, secondary to cancer elsewhere in the body, but the patient's age and lack of prior disease make this unlikely as well.

Osteosarcoma is the most probable among these malignancies, comprising over 50% of malignant bone tumors for patients younger than 20 years.[1] Ewing sarcoma is the second most common primary bone malignancy in this age-group, representing over 30% of bone cancers for children and adolescents.[2] Children are the highest risk group for both sarcomas, though neither sarcoma accounts for more than 3% of overall childhood cancers.[2] Osteosarcoma most commonly occurs in children between 13 and 16 years of age, while peak incidence of Ewing sarcoma occurs between 10 and 15 years of age.[2,3] This age dependency may be related to the adolescent growth spurt, especially as osteosarcoma often manifests near the metaphyseal growth plate.[4] In both cases, males are at higher risk than females, though the reason for this is unknown.[4]

Some benign bone tumors are capable of forming palpable masses similar to the one seen in the present patient. These include aneurysmal bone cysts (ABCs) and giant cell tumors. However, as we will see, giant cell tumors are exceedingly rare in children and adolescents.

Taking these considerations into account, the differential diagnosis includes Osgood-Schlatter, subacute osteomyelitis, myositis ossificans, osteosarcoma, Ewing sarcoma, chondrosarcoma, metastatic tumor, giant cell tumor, and ABC. At this stage, the differential is based solely on the clinical presentation. The patient's age, his large tibial mass, and his male sex have been particularly informative. A simple radiograph of the area surrounding the palpable mass, in addition to histologic data, will be important for narrowing the differential diagnosis.

Diagnostic Findings, Part II

The Patient's Radiograph Is Shown in Figure 1. Describe the Findings

Figure 1 shows a simple radiograph of the right distal femur, proximal tibia, and proximal fibula. There is an ill-defined mass in the tibial metaphyseal region expanding into the surrounding soft tissue, with "fluffy" calcification. The mass appears to be a neoplasm, as a Codman triangle—a small, triangle-shaped displacement of the periosteum which occurs as a tumor pushes through the bone cortex—can be seen in the medial cortex at the distal edge of the mass.[5] The Codman triangle is identified by a thin layer of ossification beneath a raised edge of periosteum and is indicative of bone tumors such as osteosarcoma and Ewing sarcoma. As such, non-neoplastic disorders can be eliminated from the differential. To further narrow the diagnosis, a deeper understanding of the possible neoplasms—including their radiology, histology, and epidemiology—may be of use.

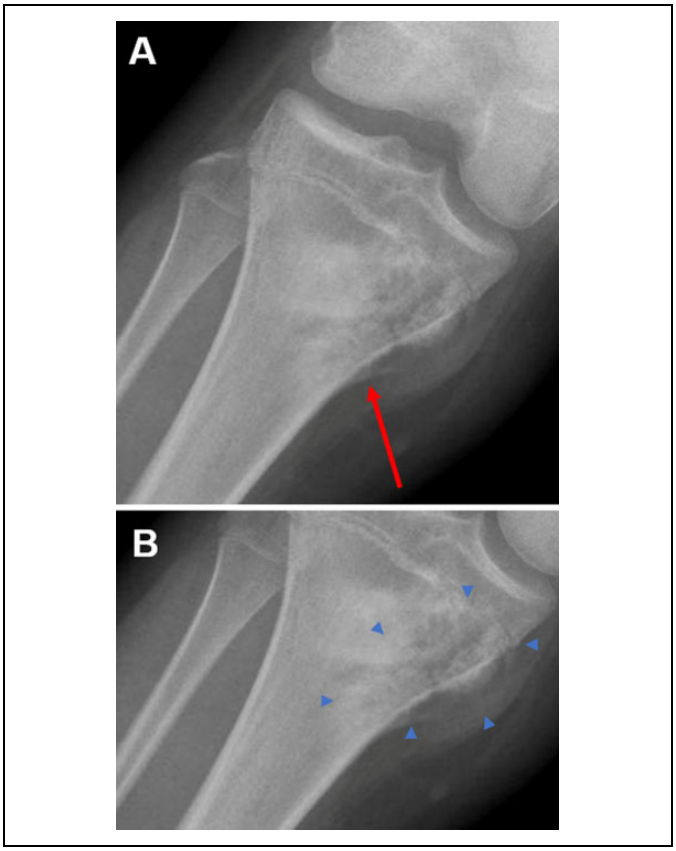

Figure 1. Simple radiograph of the right distal femur, proximal tibia, and proximal fibula. Note the large irregular mass obscuring the proximal tibial metaphysis. Red arrow denotes Codman triangle (A). Blue arrowheads delineate extension of tumor into the surrounding soft tissue (B). The mass is approximately 9 cm at its greatest dimension, according to imaging measurement of a subsequent computed tomography (CT) scan.

Question/Discussion Points, Part II

Describe the Pathological Features, Radiological Characteristics, and Clinical Courses for the Malignant Tumors Under Consideration

At the broadest level, we can delineate between primary and secondary bone tumors. Primary bone tumors originate within

bone cells and do not arise from other cancers. Secondary bone tumors arise from cancers elsewhere in the body and typically arise through metastasis. (This is different from the classification for "secondary osteosarcoma," referenced below.) Depending on the disease and stage, primary malignant bone tumors can have promising outcomes, while secondary bone tumors often carry poor prognoses.

Within the category of primary bone tumors, there exist several malignant and benign variants. Benign tumors are much more common, although malignant bone tumors represent the sixth most common childhood neoplasm and the third most common neoplasm in adolescents and young adults.[6] Approximately 2400 primary bone malignancies are diagnosed in the United States each year.[4]

Osteosarcoma is the most common primary bone malignancy in children and adolescents, representing approximately 400 new cases each year in patients younger than 20 years.[2] The malignancy is a bone-forming tumor with several subtypes, most often producing "woven" osteoid tissue in the metaphyseal regions of the distal femur or proximal tibia.[4] Tumors typically present as painful masses, which may grow larger over time. Patients rarely present with systemic symptoms such as fever or weight loss. Radiographs of osteosarcoma may depict the Codman triangle, which forms as pleomorphic osteoid-producing cells expand through the periosteum.[4] The associated soft tissue mass includes regions of both lytic and sclerotic tissue. Histology shows large, pleomorphic tumor cells with hyperchromatic nuclei and haphazard, lacelike patterns of osteoid and mature bone.[4]

Although osteosarcoma is technically a primary bone tumor, we can further delineate this malignancy into "primary" and "secondary" categories. Primary osteosarcoma is *not* directly related to prior diseases or treatments, while secondary osteosarcoma can develop from prior treatments (eg, irradiation, chemotherapy) or skeletal disorders (eg, Paget disease).[2] Regardless of origin, osteosarcomas are often assumed to have subclinically metastasized by the time a patient is diagnosed.[7] Therefore, treatment often progresses in 3 stages: neoadjuvant chemotherapy, surgical tumor resection, followed by additional chemotherapy and/or radiation. Given timely and proper therapy, two-thirds of patients with nonmetastatic primary osteosarcoma will survive long term.[2]

Ewing sarcoma is the second most common bone neoplasm in children and adolescents, accounting for over 30% of primary malignant bone tumors in this age-group.[2] About four-fifths of Ewing patients are younger than 20 years, and males are slightly more affected than females.[5]

Most often in Ewing sarcoma, primitive round cells develop into large lytic masses, producing tan-white tumors which are often palpable during the physical examination. Nearly 85% of cases involve a balanced translocation, where the $EWSR_1$ gene of chromosome 22 is fused, in-frame, to the FLI_1 gene of chromosome 11.[4] Under radiographic imaging, the resultant lytic masses appear as "moth-eaten" lesions of bone and may elicit the Codman triangle. An associated soft tissue mass may also be seen in radiographs of Ewing patients.[8] Periosteal layers may appear in an "onion peel" fashion, as the periosteum degrades into reactive layers. Histologic data typically reveal consistent groupings of small, round cells with low levels of cytoplasm.[4] In 10% to 20% of Ewing cases, patients may also have systemic symptoms such as fever, malaise, and weight loss.[5] Eighty to ninety percent of Ewing patients will relapse if treated solely with local therapy—suggesting, like osteosarcoma, that many have subclinical metastases at the time of diagnosis.[9] For clinically localized Ewing, treatment therefore involves a neoadjuvant chemotherapy, surgical resection, and adjuvant chemotherapy process similar to that osteosarcoma. When this course is followed, 5-year survival rates for Ewing can reach up to 75%.[4]

Finally, chondrosarcomas are malignant, cartilage-producing tumors, which can also be delineated into smaller categories. The most common category is conventional chondrosarcoma, which accounts for nearly 90% of all chondrosarcomas.[4] The other 10% is divided between dedifferentiated, clear cell, and mesenchymal chondrosarcoma subtypes. Like Ewing and osteosarcoma, the cartilaginous tumors of conventional chondrosarcoma can permeate the medullary cavity, producing large and painful tumors. However, unlike Ewing and most osteosarcomas (which are bone-forming), the tumor is composed of hyaline cartilage. Upon radiographic imaging, such tumors may resemble bright regions of loosely-clumped, irregular calcification. And again in contrast to the other primary bone malignancies, these are typically diagnosed in persons between 40 and 60 years of age.[4] Furthermore, conventional chondrosarcoma is most often found in the axial skeleton, particularly in the pelvic and shoulder regions.[4]

Chondrosarcomas are evaluated by a histologic grading system, which is highly relevant to their pathology and clinical course. This system is organized into 3 categories: grade 1, grade 2, and grade 3. Classifications are made based on the nuclear size, cellularity, mitotic activity, and staining patterns of histological specimens.[4] Grade 1 tumors have low to moderate cellularity; little mitotic activity; and small, round nuclei visible in the chondrocyte cells.[10] These tumors rarely metastasize, with 5-year survival rates near 80%. As a result, treatment may simply involve local resection of the tumor alongside local adjuvant treatment (such as phenolization, cryotherapy, or cementation).[10]

On the other end of the spectrum, grade 3 chondrosarcomas are highly cellular, with extreme nuclear pleomorphism and remarkable mitotic activity. In contrast to grade 1 tumors—which contain abundant hyaline cartilage—grade 3 tumors have sparse levels of chondroid matrix.[4,10] The 5-year survival rate for patients with grade 3 chondrosarcoma is only 43%, and surgical resection is rarely sufficient to prevent relapse.[4] Regardless, chondrosarcoma is an unlikely diagnosis given the patient's age and tumor localization.

Discuss the Benign Tumors Mentioned in the Differential

In theory, both giant cell tumor and ABC could produce a palpable mass like the one seen in this patient. And though the

patient is not likely suffering from either form of tumor, the possibility merits consideration.

Giant cell tumors are aggressive collections of multinucleated, osteoclast-like cells.[4] Osteoclasts—which break down and reabsorb bone tissue—are normally quite active and multinucleated. But in giant cell tumors, these cells expand through and degrade the overlying bony cortex, producing a large mass of soft tissue. These osteoclast-like cells can contain over 100 nuclei each and are interwoven with groups of smaller, uniform mononuclear cells.[4] Their resultant tumors are soft and covered by a thin layer of reactive bone, with little bone tissue inside. In simple radiographs, they appear as expansive and lytic masses which are destructive to the bone cortex. These tumors are highly variable in their clinical behavior, though most are found in the distal femur or proximal tibia, and can be resected through curettage. Although the size and location of this patient's tibial mass correspond to those of giant cell tumors, such tumors are exceedingly rare in children and adolescents. Therefore, the patient is not likely suffering from a giant cell tumor.

Aneurysmal bone cysts most often present in the metaphysis of the long bones in patients younger than 20 years.[4] These tumors are actually blood-filled cystic bodies, surrounded by fibrous walls which contain osteoblasts, osteoclasts, and woven bone tissue. The cysts are expansive and can rapidly degrade bone tissue, while also eliciting painful swelling. Radiographically, they appear as circumscribed "soap bubbles" or "egg shells," with thin sclerotic rims surrounding the lesion, and fluid levels indicative of blood within the cystic space. Excision or curettage are the most effective treatments, though cysts can still recur afterward. Given this patient's age, alongside his tumor location and size, one might be inclined toward a diagnosis of ABC. However, the typical ABC—with its "egg shell" appearance and high fluid levels under radiographic imaging—contrasts starkly with the mass seen in Figure 1. As such, the patient is not likely suffering from an ABC, reaffirming the likelihood of a malignant neoplasm.

Might This Patient Have a Secondary (Metastatic) Bone Tumor?

Secondary bone tumors carry very poor prognoses, yet are much more common than primary bone tumors.[4] However, the patient is not likely suffering from a secondary tumor. Firstly, because metastatic bone tumors rarely occur in the tibia—a majority occur in the axial skeleton, especially in the vertebral column.[4] (The patient has no indication of neoplasia in the axial skeleton, though a full-body positron emission tomography [PET] scan would be necessary to rule this out.) Secondly, most secondary bone tumors have metastasized from a few characteristic neoplasms. In adults, these are malignancies of the breast, lungs, thyroid, kidneys, and prostate; in children, they are neuroblastoma, Wilms tumor, and rhabdomyosarcoma.[4] Because the patient has not suffered from any malignancy prior to the clinical presentation, he is very unlikely to have a secondary bone tumor. (It is important to note the difference between secondary *bone tumors* and secondary *osteosarcoma*, mentioned above.) Nonetheless, a full-body PET scan could be used to identify possible primary cancers elsewhere in the body.

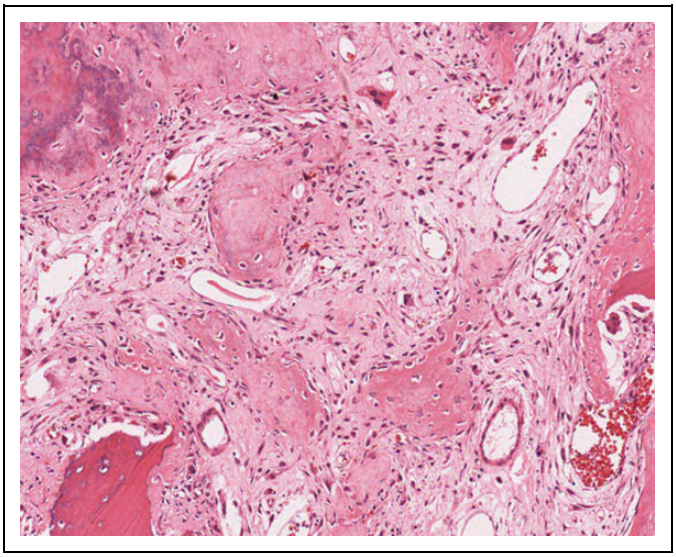

Figure 2. Histological slide from core needle biopsy of the right proximal tibia. Note the woven, haphazard arrangement of osteoid tissue and immature bone. Bottom left-hand corner shows region of darker, matured lamellar bone. Upper left-hand corner shows region of immature, ossifying tissue, more organized than surrounding light-pink osteoid material. Magnification = ×80.

What Further Testing Is Indicated for This Patient?

Histological data are necessary to form an accurate diagnosis. These data could be acquired through either an open biopsy or a core needle biopsy. A full-body PET scan should also be ordered to rule out metastases and to confirm that the bone tumor is not secondary to another cancer elsewhere in the body.

Diagnostic Findings, Part III

The PET Scan Reveals No Clinical Metastases. A Core Needle Biopsy Is Performed, Yielding the Histological Specimen of Figure 2. Describe the Findings, and How They Influence Your Diagnosis

The histological image shows spindle-like, pleomorphic bone-forming cells, characteristic of a malignant neoplasm. Loosely woven pink osteoid tissue occupies most of the image, suggesting that these are osteoid-producing cells. (One can tell osteoid tissue from normal bone, by identifying the lighter, less-organized immature proteinaceous material.) In the bottom left-hand corner, darker, solid red tissue indicates more mature bone. This can be seen from the apparent mineralization (leading to darker appearance) and characteristic lamellae. Early ossification is occurring in the upper left-hand corner, shown by the moderately darkened and partially mineralized tissue.

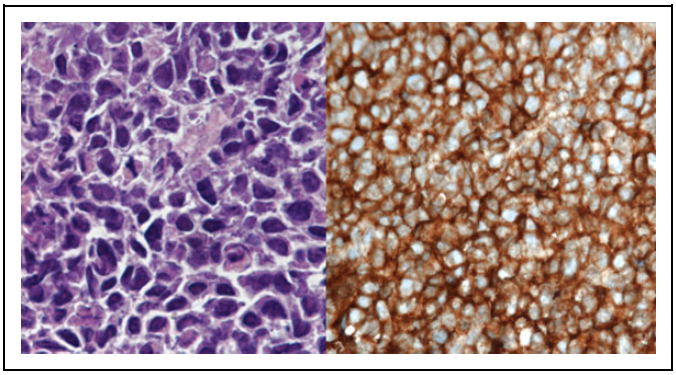

Figure 3. Histological slide typical of Ewing Sarcoma (left) and Ewing Sarcoma under CD99 immunohistochemical staining (right). Note the monotonous presence of immature small round cells, as well as the high nucleus to cytoplasm ratio. Magnifications = ×400.

As a whole, the image shows haphazard arrangements of mature and immature bony material. Clearly, this is a malignant sarcoma which has been producing irregular osteoid tissue. In combination with the radiograph from Figure 1, this is likely an osteosarcoma. Given that this patient has no other clinically notable tumors, the osteosarcoma is a primary neoplasm.

Question/Discussion Points, Part III

What Would You Have Expected to See If This Were an Ewing Sarcoma?

If this patient had Ewing, one would *not* expect to see pleomorphic cells surrounded by irregular osteoid tissue. Instead, one would expect consistent groupings of small round cells, each about the size of a lymphocyte.[5] These cells would have a very high nucleus to cytoplasm ratio, with minimal sign of stroma, giving a characteristically dark stain to the resulting image. Figure 3 provides an example of this. Additionally, Ewing sarcoma cells are positive for CD99 by immunohistochemical staining, because their cell surfaces contain the CD99 antigen which is bound by the stain.

Even Though Osteosarcoma Is the Most Common Childhood Malignant Bone Neoplasm, It Still Accounts for Just 3% of Childhood Cancers. What Risk Factors Might Have Predisposed This Patient to the Disease?

Before delving into specific risk factors, one might revisit the difference between primary and secondary osteosarcoma. Primary osteosarcoma, like other primary bone tumors, originates in bone cells and is not directly associated with another cancer or disease. Secondary osteosarcoma also originates in bone cells but is associated with either a skeletal disease or treatment from another condition (typically cancer). Perhaps confusingly, both forms are considered "primary bone tumors," because both arise from bone cells themselves. Nonetheless, primary osteosarcoma is the predominant form in children and adolescents.

Genetic predisposition likely plays a role in childhood primary osteosarcoma. For example, approximately 70% of sporadic osteosarcoma tumors contain acquired mutations in *RB*, the negative cell cycle regulator.[4] Most commonly, these are loss-of-heterozygosity mutations, though point mutations also contribute.[11] Germline *RB* mutations also play a role, increasing osteosarcoma risk 1000-fold.[4]

Inactivation of *TP53*, which codes for a protein critical to apoptosis and DNA repair, has also been linked to osteosarcoma.[2,4,12] For instance, patients with Li-Fraumeni syndrome (characterized by germ line inactivation of *TP53*) can suffer from osteosarcoma in addition to a multitude of other cancers. Inactivation of the *$CDKN_2A$* gene—which codes for p14 and p16, 2 proteins involved in tumor suppression—also increases risk for osteosarcoma. This occurs through 2 respective pathways: those of p53 and Rb, respectively.[11] With the former, p14 functions to inhibit degradation of p53 (the product of *TP53*) by sequestering the E3 ubiquitin ligase to the nucleolus, thereby preventing ubiquitin tagging of p53. In the latter, p16 acts as negative regulator of CDK4, which typically phosphorylates Rb (the product of *RB*). When CDK4 does phosphorylate Rb, the cell cycle is allowed to progress from G_1 to S phase; inactivation of p16, therefore, keeps this checkpoint constitutively open.[11,12] (It is important to note that loss-of-function mutations in *RB*, referenced above, can remove this checkpoint entirely.)

Unlike Ewing sarcoma, there is no characteristic translocation—or any canonical genetic mutation—associated with osteosarcoma.[4,11] However, the latter neoplasia has recently been linked to chromosomal instability (CIN), a heterogenous, genome-wide set of chromosomal alterations, which impacts the number of chromosomes or sections within chromosomes.[11] In turn, CIN itself arises from dysfunction in the cell cycle and DNA repair processes, partially explaining the importance of genes such as *RB* and *TP53* in osteosarcoma.

As noted, a host of chromosomal alterations play a role in CIN-related osteosarcoma. For instance, chromosomes 3, 6, 9, 10, 13, 17, and 18 contain common locations for deletion events which impact copy number variation in osteosarcoma cells.[1] These regions are notable for encoding numerous tumor suppressors, explaining why such deletions may increase risk for osteosarcoma.[11,12] On the other hand, chromosomes 1, 6, 7, and 17 contain notable oncogenes and are the most common sites for amplification in osteosarcoma-related copy number alterations.[12] These complex rearrangements have potential for widespread genetic variations, even between osteosarcoma cells. As a result, the genetic etiology of osteosarcoma remains unknown, and the search for targeted molecular treatments remains unsuccessful.[11,12]

Prior irradiation—from an earlier primary cancer, for instance—increases risk for secondary osteosarcoma and may be responsible for approximately 3% of osteosarcomas.[2] Exposure to chemotherapy heightens this effect.[2] The incidence of irradiation- and chemotherapy-related secondary osteosarcoma

may only increase with time, as survival rates rise for certain childhood cancers.

Because 75% of osteosarcoma cases occur in persons younger than 20 years, much attention is paid to the risk factors for children and adolescents.[4] But in truth, osteosarcoma displays a bimodal age distribution, with older adults comprising a smaller, yet still significant proportion of cases. Interestingly, adult patients are more likely to develop osteosarcoma in the axial skeleton, and patients over 60 years old are at highest risk for metastatic tumors. In contrast to their younger cohorts, these patients often suffer from *secondary* osteosarcoma, typically associated with Paget disease. Paget, notable for its accelerated and disordered pattern of bone turnover, occurs in 1% of US adults older than 40 years.[4] Just fewer than 1% of Paget patients will undergo sarcomatous transformation of the disease, leading to secondary osteosarcoma.[2] In polyostotic cases of Paget (ie, cases involving multiple bones), this figure increases to 5% to 10%.[4]

Now That You Have Diagnosed the Patient With Primary Osteosarcoma, How Do You Stage the Cancer?

Bone sarcoma staging guidelines, set by the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control, operate using the TNM staging system.[2,13] In this system, tumors are evaluated for their size and extent (T), lymph node involvement (N), and metastases (M). There is also a category for histological grade (G). Each category contains a set of grades, depending on the type of tumor (eg, bone sarcomas). For instance, bone sarcomas in the appendicular skeleton have 5 grades for tumor extent: TX (primary tumor not assessable), T0 (no evidence of primary tumor), T1 (tumor $\leq$8 cm at greatest dimension), T2 (tumor $\leq$8 cm at greatest dimension), and T3 (discontinuous tumors in the primary bone site). Tumors are also evaluated for their absence (N0) or presence (N1) of regional lymph node metastases, alongside their absence (M0) or presence (M1) of distant metastases. If distant tumors have metastasized to the lung, they are classified at M1a, while metastases to the bone or other distant sites are classified as M1b. Finally, histological specimens are considered well differentiated and low grade (G1), moderately differentiated and high grade (G2), or poorly differentiated and high grade (G3). Finally, the AJCC provides a framework for assigning an overall "stage group" based on these collective classifications.[13]

According to imaging analysis, the patient's tumor is approximately 9 cm at its greatest dimension (Figure 1), making it a T2 bone sarcoma. The full-body PET scan revealed no metastases, qualifying as both N0 and M0. Finally, the histology appears to be moderately differentiated, indicating a G2 grade. Taken together, these classifications place the tumor in the II-A stage group. One should note that the tumor has been staged using "clinical staging" practices, which do not include surgical measurement. A "pathological stage" could be reached by incorporating data from surgical exploration or from removal of the tumor. These pathological data do, at times, alter the conclusions of clinical staging.

The Musculoskeletal Tumor Society (MSTS) provides separate staging guidelines for bone sarcomas.[14] The MSTS guidelines categorize malignant bone tumors by grade: stage I (low grade), stage II (high grade), and stage III (tumors with distant metastases). Within each stage, tumors are characterized as type A tumors (intracompartmental, contained within the bone cortex) and type B (extracompartmental, extending beyond the cortex). The final stage is used for surgical decision-making, with no impact on chemotherapeutic approach.

Given the lack of clinically notable metastases, this tumor is either stage I or stage II. The tumor is large, and histology shows a marked proliferation of osteoid cells, suggesting that this is a high-grade stage II tumor. Furthermore, the tumor has clearly lifted the periosteum (demonstrated by the Codman triangle) and expanded into the surrounding soft tissue. The patient can therefore be diagnosed with a stage II-B primary osteosarcoma when regarding the MSTS guidelines.

Briefly Describe the Therapeutic Approaches for This Patient

As noted, the treatment of primary osteosarcoma typically involves 3 stages: neoadjuvant chemotherapy, surgical resection of the tumor, and adjuvant chemotherapy. In the absence of clinically detected metastases, 5-year survival rates range between 60% and 70%.[2,4] When chemotherapy is excluded, however, up to 80% of patients will develop metastatic tumors (even if the original cancer is locally controlled).[2] This patient should, therefore, follow the standard 3-stage protocol.

There is no consensus on the ideal chemotherapy for bone sarcomas. Nonetheless, the American Osteosarcoma Study Group (AOST) has put forth the MAP regimen, which uses methotrexate, doxorubicin, and cisplatin for both neoadjuvant and adjuvant therapy.[15] In the AOST protocol, the neoadjuvant phase lasts for 10 weeks, surgery is performed in week 11, and adjuvant therapy resumes for weeks 12 through 29. A leucovorin rescue can be used alongside high-dose methotrexate.

Between the neoadjuvant and adjuvant chemotherapy, there are 2 main surgical approaches. The first is amputation of the affected region; the second is limb-sparing resection of the tumor. (With tumors of the metaphyseal region, resection is typically "osteoarticular," removing the tumor, the tumor-bearing bony portion, and portions of the adjacent joint.)[16] Oncologic outcome is of primary concern when choosing a surgical approach, and functional outcomes are secondary. If complete excision of the tumor is anatomically impossible, or otherwise complicated, amputation remains the "gold standard" to avoid recurrence and metastasis.[16] Nonetheless, the use of limb-sparing resections has increased with the employment of effective chemotherapy. And regardless of approach, the level of chemotherapy-induced tumor necrosis found during surgery is highly relevant to long-term prognosis.[4,16]

Given this patient's age, activity level, and lack of clinical metastases, limb-sparing surgery is preferable to amputation. However, the patient will likely require reconstructive surgery. An allograft or expandable endoprosthesis may be suitable for his immature skeleton, allowing for equal development of his lower limbs.

If initial treatment is deemed successful, the National Comprehensive Cancer Network recommends follow-up surveillance every 3 months for years 1 to 2, every 4 months during year 3, every 6 months for years 4 to 5, and once annually from year 6 onwards.[15] While there is no established time line for the duration of follow-up, most bone sarcoma recurrences occur within 10 years of treatment.[15]

Teaching Points

- Radiographs of osteosarcoma typically depict a soft tissue mass, including lytic and sclerotic tissue, alongside the notable Codman triangle.
- Bone tumors can be classified as primary (originating in the bone itself) or secondary (having metastasized from elsewhere in the body).
- Osteosarcoma and Ewing sarcoma are the most common primary malignant bone tumors in children and adolescents.
- Osteosarcomas are malignant bone-forming tumors which produce woven osteoid tissue and comprise 50% of all childhood bone neoplasms.
- Histology of osteosarcoma shows haphazard arrangements of loosely woven osteoid tissue, surrounded by sections of mature lamellar bone.
- While there is no established genetic etiology of osteosarcoma, CIN is common among osteosarcoma cells.
- Giant cell tumors are soft, benign collections of multinucleated osteoclast-like cells, which appear near the epiphysis of the long bones.
- Aneurysmal bone cysts are benign, blood-filled cystic bodies which typically appear as "egg shell" masses near the metaphysis of the long bones.
- Malignant bone tumors are staged after diagnosis and before treatment. The specific stage of any given tumor will influence the prognosis and treatment of that cancer.
- In the AJCC guidelines, bone sarcomas are evaluated for tumor extent (T), lymph node involvement (N), distant metastases (M), and histologic grade (G). They are then given an overall "stage group" (stages I-IV, subgroups A-B) based on these evaluations.
- In the MSTS guidelines, bone sarcomas are staged by their grade (stages I-III) and whether they are intracompartmental (A) or extracompartmental (B).
- Clinical staging of a tumor can be reached through imaging or other nonsurgical measurements, while pathological staging requires surgical exploration or removal of the tumor.
- Treatment for osteosarcoma typically involves neoadjuvant chemotherapy, surgical removal of the tumor, and adjuvant chemotherapy.
- Chemotherapy of osteosarcoma often follows the MAP regimen—methotrexate, doxorubicin, cisplatin—for both neoadjuvant and adjuvant phases.

Declaration of Conflicting Interests

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Educational Case: Head and Neck Neoplasia: Salivary Gland Tumors

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, head and neck neoplasia, salivary gland tumor, warthin tumor, pleomorphic adenoma, mucoepidermoid carcinoma

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Primary Pathology Learning Objective

Objective HN2.1. Benign and Mucoepidermoid Tumors of Salivary Glands. Distinguish the clinicopathologic features of the 2 benign tumors (pleomorphic adenoma or mixed tumor and Warthin tumor) from the malignant mucoepidermoid carcinoma.

Competency 2: Organ System Pathology, Topic: Head and Neck (HN), Learning Goal 2: Head and Neck Neoplasia

Secondary Pathology Learning Objective

Objective CYP1.2. Categorizing Diagnostic Certainty: Compare and contrast the degree of diagnostic certainty applied to general diagnostic categorization in cytologic diagnosis.

Competency 3: Diagnostic Medicine and Laboratory Diagnosis; Topic CYP: Cytopathology; Learning Goal I: Cytologic Diagnosis

Patient Presentation

A 62-year-old obese, hypertensive, Caucasian male presents to his primary care physician with a slowly growing left cheek mass for 1-year duration. He has a 40 pack-year smoking history. He has no family or personal history of carcinoma. He is HIV-negative and has not experienced any dysphagia, odynophagia, B-symptoms, trismus, or facial weakness.

Diagnostic Findings, Part 1

On physical examination, his primary care physician notes a palpable, 2 cm, "doughy," mobile mass in his left parotid gland. There appears to be mild erythema and slight puckering of the skin overlying the mass. The contralateral parotid gland has no palpable masses and there is no cervical lymphadenopathy. Tongue sensation and facial nerve function are intact. The patient undergoes imaging studies and fine needle aspiration (FNA) biopsy of his lesion.

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Questions and Discussion Points, Part 1

Given the Clinical History, What Are the Most Likely Salivary Gland Neoplasms This Patient Might Have, and What Clinical Features Would Suggest Each Diagnosis?

Salivary gland tumors are rare, making up less than 2% of all tumors. Up to 80% of salivary gland tumors appear in the parotid gland, and 70% of parotid gland tumors are benign. Parotid gland neoplasms are more likely to be benign than submandibular gland neoplasms, which are more likely to be benign than minor salivary gland neoplasms, which are more likely to be benign than sublingual gland neoplasms. Although certain clinical features can be suggestive, they are unreliable to definitively differentiate between benign or malignant.[1,2]

The most common salivary gland tumor is pleomorphic adenoma and makes up approximately 50% of all salivary gland tumors and 80% of all benign salivary gland tumors. They typically are painless, mobile, and slow growing and occur most frequently in the parotid gland—features all seen in our patient. However, pleomorphic adenoma occurs more frequently in females, and the average age of presentation is in the mid-40s—unlike our patient.[1-3]

Warthin tumor is the second most common salivary gland neoplasm and occurs almost exclusively in the parotid gland. It is seen more frequently in male patients, the average age of presentation is in the mid-60s, and it has a strong correlation with smoking history. In addition, the "doughy" texture of the mass is a frequent finding in Warthin tumor. Up to 10% of Warthin tumors are multifocal, and up to 15% of Warthin tumors occur bilaterally, so either of these features would also raise the suspicion for this diagnosis.[1,2] However, our patient's lack of a contralateral mass on physical examination certainly does not rule out this diagnosis.

Mucoepidermoid carcinoma is the most common malignant salivary gland neoplasm. It affects a broad age range and is the most common primary malignant salivary gland tumor in both adults and children. It is likely to demonstrate symptoms related to its invasive nature, including rapid growth, pain, immobility, skin changes and facial asymmetry, cervical lymphadenopathy, and loss of nerve function.[1,2] The patient demonstrated few of these concerning symptoms (mild erythema and slight puckering overlying the mass) and the diagnosis is lower on the differential.

In summary, the differential diagnosis includes but is certainly not limited to pleomorphic adenoma, Warthin tumor, and mucoepidermoid carcinoma. The skin erythema and puckering may be seen in a malignant process (mucoepidermoid carcinoma); however, the mobility, painlessness, slow growth, and absent lymphadenopathy suggest a benign tumor (Warthin tumor or pleomorphic adenoma). These features combined with the "doughy" texture, patient's smoking history, male sex, and patient age suggest a Warthin tumor.

What Risk Factors Predispose a Patient to Develop Salivary Gland Neoplasms?

Ionizing radiation, in the form of atomic bomb exposure, previous head and neck radiation therapy, and radioactive iodine treatment for thyroid disease, have all shown an increased association with the development of salivary gland neoplasms. There is also a strong association with smoking and the development of Warthin tumor—smokers are 8 times more likely to have a Warthin tumor than the general population. Certain genetic alterations occur more frequently in certain salivary gland tumors but familial aggregation has not yet been observed in salivary gland tumors.[1]

What Diagnostic Testing Is Available for This Patient?

Although the clinical history and certain physical examination findings, such as mobility of the mass or overlying skin changes, can suggest a benign or malignant process, computed tomography, magnetic resonance imaging (MRI), and ultrasonography are much more accurate. Imaging is primarily used to assess malignant features, rather than to ascertain a specific diagnosis. Imaging studies can determine if a neoplasm is contained within the salivary gland or if it has invaded into adjacent structures. It can also assess regional lymph node and distant metastases. However, a tissue biopsy is ultimately required to make a diagnosis in salivary gland tumors. Tissue biopsy can be performed via fine needle aspiration biopsy or core needle biopsy.[2]

What Are the Advantages and Limitations of Fine Needle Aspiration in Presurgical Assessment of Salivary Gland Tumors?

Salivary gland tumors are a heterogeneous and morphologically diverse group of benign and malignant neoplasms. They are often sampled by fine needle aspiration and/or core needle biopsy, but given the significant overlap in morphology and immunohistochemical staining between salivary gland tumors, tissue biopsy still has limitations in its ability to confer a definitive diagnosis. Accuracy of FNA diagnosis varies across studies and practitioners. Generally, cytologic sampling has approximately 96% to 98% sensitivity in identifying a salivary gland neoplasm, with 79% sensitivity and 96% specificity in distinguishing benign from malignant tumors. Even in the absence of a definitive diagnosis, however, tissue biopsy can still help narrow down the differential, making it a valuable tool in triaging patients for medical or surgical management. Core biopsy may offer better accuracy than FNA biopsy, but it also causes more discomfort to the patient and has greater risk of complications, such as nerve damage and tumor seeding along the needle tract.[4]

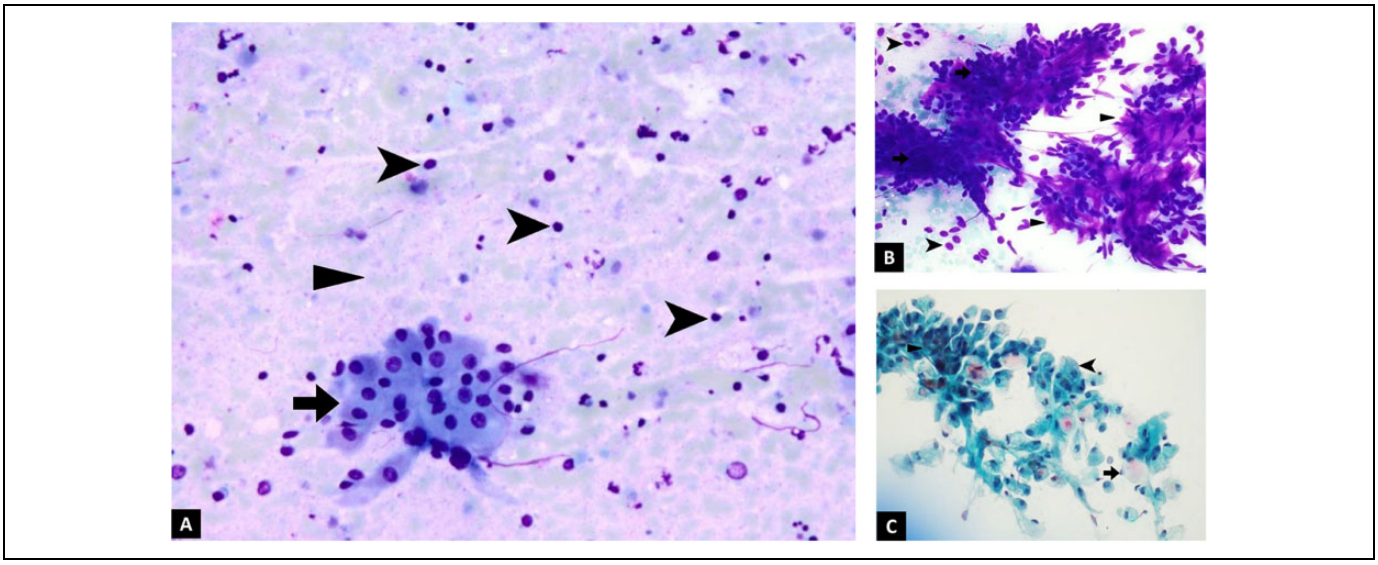

Figure 1. Cytologic features. A, FNA biopsy of the patient's lesion, showing Warthin tumor with sheets and clusters of oncocytic cells (arrow), lymphocytes (arrowhead), and granular debris in the background (triangle). B, Cytology of pleomorphic adenoma for comparison, with cohesive sheets and clusters of ductal cells (arrow), individual myoepithelial cells (arrowhead), and metachromatic, magenta-colored, fibrillary stroma (triangle). C, Cytology of mucoepidermoid carcinoma for comparison, with signet-ring type mucin producing cells (arrow), polygonal squamoid cells with dense blue cytoplasm (arrowhead), and smaller intermediate cells (triangle).

Diagnostic Findings, Part 2

Magnetic Resonance Imaging

The patient undergoes MRI of the neck with and without contrast, which demonstrates 2 enhancing parotid masses located in the superficial lobe of the left parotid gland. The masses measure 1.2 × 0.8 × 0.9 cm and 0.7 × 0.6 × 0.5 cm. The deep parotid lobes are not involved. The right parotid gland is unremarkable. No infiltrative features or cervical lymphadenopathy are seen.

Cytologic Assessment

Upon biopsy of the larger lesion, thick, green-brown fluid is aspirated, resembling motor oil. A representative photomicrograph of the FNA biopsy of the patient's larger lesion is shown in Figure 1A.

Questions and Discussion Points, Part 2

How Do the Findings on MRI Help Narrow Down the Differential?

Since no infiltrative features or cervical lymphadenopathy are seen, a benign neoplasm is favored. On imaging, the tumor was found to be 2 separate nodules, rather than a solitary lesion that was noted on physical examination. The clinical presentation plus the features seen on radiology (multiple lesions with no infiltrative features) make a diagnosis of Warthin tumor likely.

Discuss the Cytologic Features of the Fine Needle Aspirate Biopsy in Figure 1A

The "motor oil" fluid that is aspirated from the lesion is a common feature of Warthin tumor. The biopsy of the tumor has 3 distinct features, which are diagnostic of Warthin tumor: sheets and clusters of oncocytic cells (arrow), lymphocytes (arrowhead), and granular debris in the background (triangle).

The Cytologic Features of the 2 Other Neoplasms Considered in the Differential Diagnosis Are Shown in Figure 1B and C for Comparison. What Features Distinguish the Patient's Warthin Tumor From Pleomorphic Adenoma and Mucoepidermoid Carcinoma?

Figure 1B: Pleomorphic adenoma: This tumor has cohesive sheets and clusters of ductal cells (arrow), individual myoepithelial cells (arrowhead), and metachromatic, magenta-colored, fibrillary stroma (triangle) when stained with a modified Wright Giemsa (Diff Quik) stain.

Figure 1C: Mucoepidermoid carcinoma: This tumor has a mixed population of cells, with 3 distinct cell types. Signet-ring type mucin producing cells with pink mucin (arrow), polygonal squamoid cells with dense blue cytoplasm (arrowhead), and smaller intermediate cells (triangle) when stained with a Papanicolaou stain.

What Are the Treatment Options for the Patient?

Treatment recommendations are currently based on retrospective reviews and not randomized clinical trials. Complete surgical resection with negative margins is the gold standard, and patients with benign tumors (such as Warthin tumor and pleomorphic adenoma) and low-grade tumors can be treated by surgery alone. High-grade tumors, tumors with positive resection margins, and tumors with high-risk features are usually treated with surgery

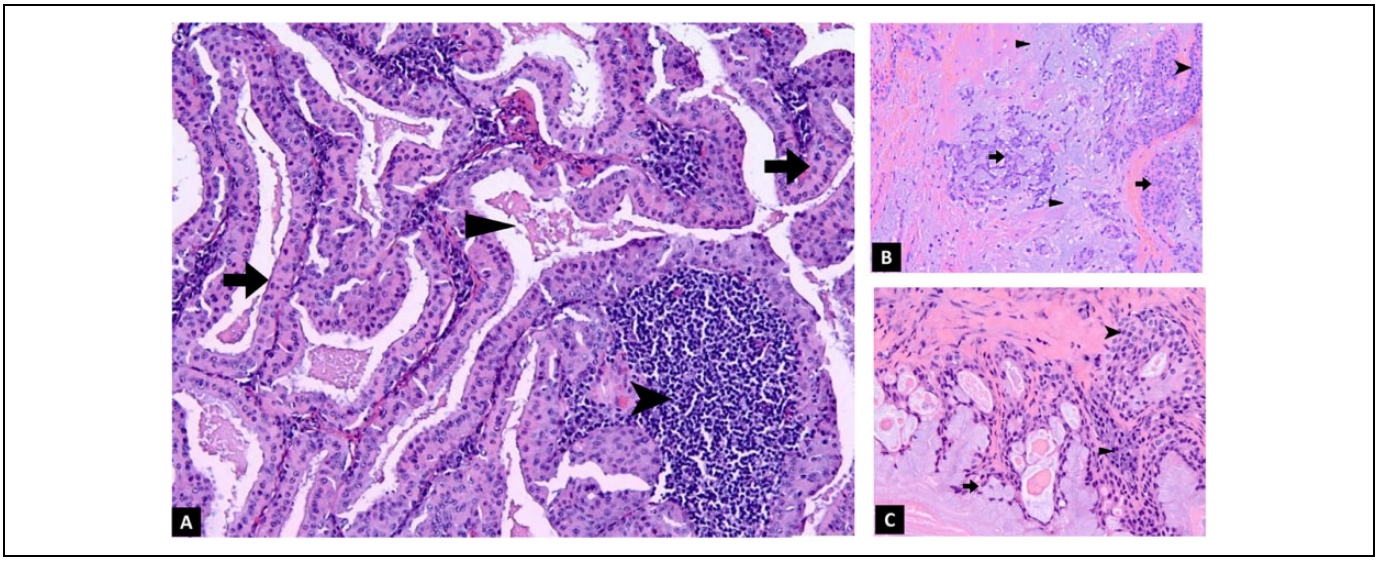

Figure 2. Histologic features. A, Surgical excision of the patient's lesion showing Warthin tumor with oncocytic cells (arrow) and lymphoid stroma (arrowhead). Granular debris fills the cyst spaces (triangle). B, Histology of pleomorphic adenoma for comparison, with ductal cells (arrow) surrounded by a layer of myoepithelial cells (arrowhead), arranged in a chondromyxoid stroma (triangle). C, Histology of mucoepidermoid carcinoma for comparison, with mucin producing cells (arrow), squamoid cells (arrowhead), and intermediate cells (triangle).

and adjuvant radiation therapy. Because he has a benign diagnosis of Warthin tumor, he can be treated with surgery alone.[5]

Diagnostic Findings, Part 3

Histologic Assessment

The patient undergoes superficial parotidectomy to remove the 2 masses. A representative photomicrograph of the patient's lesions is shown in Figure 2A.

Questions and Discussion Points, Part 3

Discuss the Histologic Features of the Surgical Excision in Figure 2A

The cystic lesion is lined by oncocytic cells (arrow) with a lymphoid stroma (arrowhead). Granular debris fills the cyst spaces (triangle). These are diagnostic of and consistent with the initial biopsy diagnosis of Warthin tumor.

The Histologic Features of the 2 Other Neoplasms Considered in the Differential Diagnosis Are Shown in Figure 2B and C for Comparison. What Features Distinguish the Patient's Warthin Tumor From Pleomorphic Adenoma and Mucoepidermoid Carcinoma?

Figure 2B: Pleomorphic adenoma: This tumor has ductal cells (arrow) surrounded by a layer of myoepithelial cells (arrowhead), arranged in a chondromyxoid stroma (triangle).

Figure 2C: Mucoepidermoid carcinoma: This cystic tumor has a mixed population of cells, with 3 distinct cell types—mucin producing cells (arrow), squamoid cells (arrowhead), and intermediate cells (triangle).

What Is the Expected Outcome After Superficial Parotidectomy to Excise the Patient's Warthin Tumor?

Surgical excision of Warthin tumor is curative, and we expect the patient to have a good clinical outcome. The risk of local recurrence after complete surgical excision is less than 2%.

The other tumors on our initial differential behave quite differently. Pleomorphic adenoma is also benign but has a higher local recurrence rate of up to 5% if treated by parotidectomy, and up to 25% if treated with simple enucleation. The behavior of mucoepidermoid carcinoma depends on the grade of the neoplasm. Local recurrence rates range from 15% to 30%, and 5-year survival ranges from 50% to 90%.[1,2]

Teaching Points

1. Salivary gland neoplasms are rare, accounting for less than 2% of all tumors.
2. Up to 80% of salivary gland neoplasms occur in the parotid gland, and up to 70% of parotid gland tumors are benign.
3. The likelihood of malignancy in each salivary gland in increasing order is: parotid gland, submandibular gland, minor salivary gland, and sublingual gland.
4. Clinical features are not definitively diagnostic of a benign or malignant process. Malignant tumors are suggested by rapid growth, pain, immobility, skin changes and facial asymmetry, cervical lymphadenopathy, and loss of nerve function. Benign tumors are suggested by absence of pain, mobility, slow growth, absence of nerve involvement.

5. Radiologic studies can provide important clues to the nature of a salivary gland tumor, including invasion beyond salivary gland parenchyma into adjacent structures and local lymphatic spread.
6. Fine needle aspiration biopsy of salivary gland tumors is an important initial diagnostic test that can frequently give an accurate diagnosis. When a specific diagnosis cannot be rendered, cytologic analysis can give a differential diagnosis that helps guide clinical/surgical management.
7. The 3 most common salivary gland tumors (pleomorphic adenoma, Warthin tumor, and mucoepidermoid carcinoma) have distinct cytologic and histologic appearances.
8. The most common salivary gland neoplasm is pleomorphic adenoma, a benign tumor that typically presents in the mid-40s and has a female predilection.
9. The second most common benign salivary gland neoplasm is Warthin tumor, which commonly presents in male smokers in their mid-60s. On physical examination, it has a "doughy" texture and can be multifocal or occur bilaterally. On aspiration, it produces a "motor oil" like fluid.
10. The most common malignant salivary gland neoplasm is mucoepidermoid carcinoma. It occurs over a broad age range and is the most common salivary gland malignancy in adults and children.
11. Pleomorphic adenoma and Warthin tumor can both be treated by surgical excision alone and have less than 5% risk of local recurrence.
12. The treatment and outcome of mucoepidermoid carcinoma is dependent on the tumor grade. High-grade tumors may require surgery and adjuvant radiation therapy, with local recurrence rate as high as 30%, and 5-year survival of 50%.

Declaration of Conflicting Interests

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Educational Case: Cervical Neoplasia: HPV and Its Link to Cancer

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, disease mechanisms, HPV, human papillomavirus, cervical cancer, neoplasia, disease screening, PAP smear

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Primary Objective

Objective N3.1: Morphologic Features of Neoplasia: Describe the essential morphologic features of neoplasms and indicate how these can be used to diagnose, classify, and predict biological behavior of cancers.

Competency 1: Disease Mechanisms and Processes; Topic N: Neoplasia; Learning Goal 3: Characteristics of Neoplasia.

Secondary Objectives

Objective CYP2.1 Screening: Describe the principles of an effective screening test and the uses and limitations of cytology.

Objective CYP2.2 Adjunct testing (HPV): Describe how adjunct testing is used in conjunction with cytology examination.

Objective CYP2.3 Cervical Screening: Describe how to find and utilize current algorithms for management of cervical screening.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic CYP: Cytopathology; Learning Goal 2: Advantages of Cytopathology.

Patient Presentation

A 45-year-old female presents to her new primary care physician to establish care after not visiting a doctor for 10 years. She was recently referred for a follow-up visit after receiving an abnormal liquid Pap result from a free community outreach cervical cancer screening program. She denies any significant past medical or surgical history. The patient's last menstrual period was 2 weeks ago, and she is currently sexually active with multiple partners. She occasionally uses barrier methods of contraception. Physical examination and pelvic examination are within normal limits. Before discussing the results, the patient remembers having a history of abnormal pap smears that required further testing, but these were not pursued since she was lost to follow-up.

Diagnostic Findings

Upon further review of the patient's history, the patient was 35 years old at the time of her last Pap test and pelvic examination. Cytology of her old Pap test showed a low-grade squamous intraepithelial lesion (LSIL). Human papillomavirus

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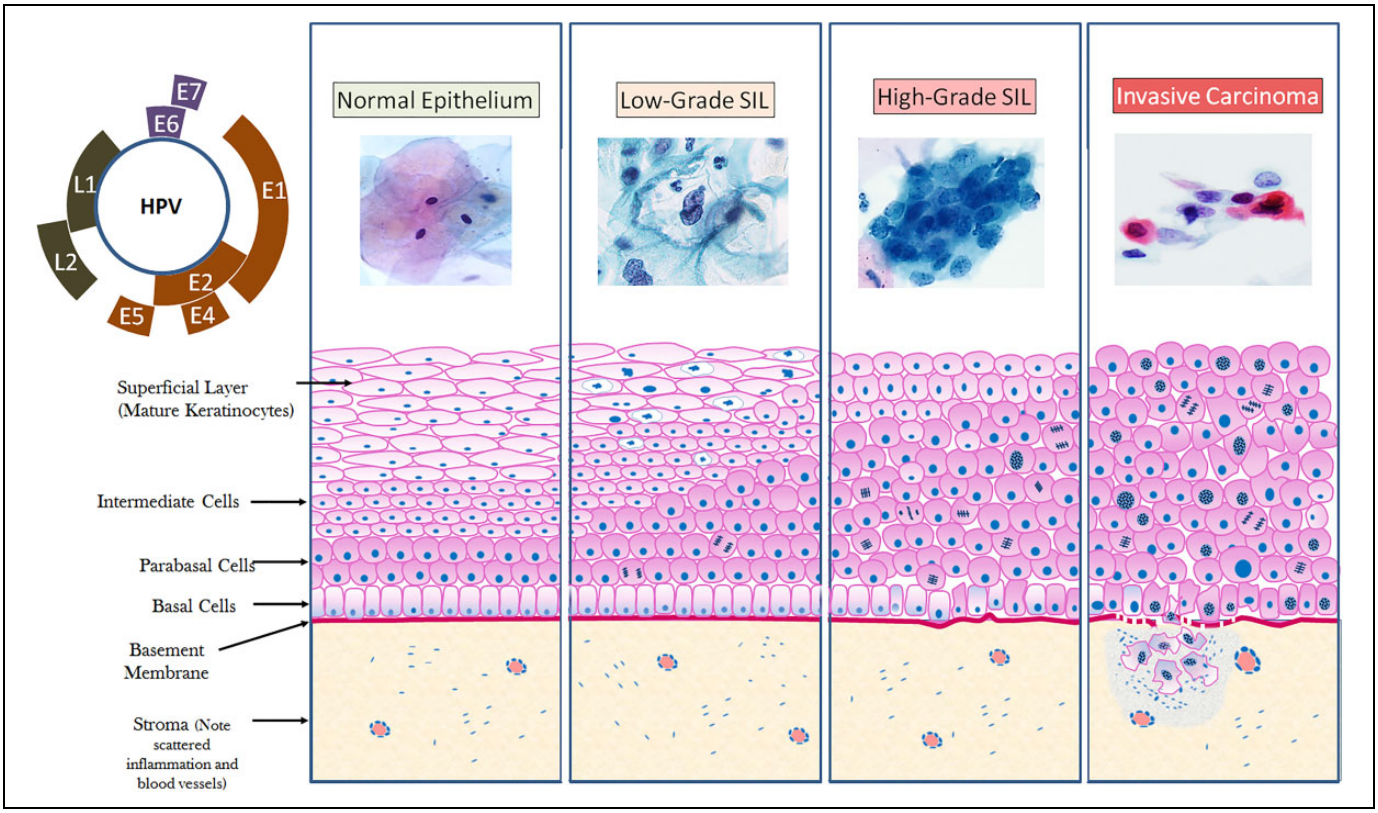

Figure 1. Sketch demonstrating the progressive nature of the dysplastic changes leading to the development of cancer. To the left is a representation of the HPV genome with its associated early and late antigen proteins. HPV indicates human papillomavirus.

(HPV) co-testing results from that time demonstrated positivity for HPV type 16. As per American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines, the patient was recommended to undergo further testing with colposcopy but was lost to follow-up.

The patient's current cytologic evaluation is consistent with high-grade squamous intraepithelial lesion (HSIL), and HPV testing remains positive for HPV type 16. Gonorrhea/chlamydia testing is negative. The patient is now scheduled for an immediate colposcopy and loop electrosurgical excision (LEEP).

Questions/Discussion Points

What Are Your Preliminary Working Diagnosis and Its Differential?

This patient cytology results previously demonstrated an LSIL, which has since progressed to an HSIL with persistent HPV infection. The SILs are virally driven neoplastic proliferations of cervical epithelial cells and are precancerous. Epidemiological studies have demonstrated the time-dependent progressive nature of these lesions (Figure 1). The differential diagnosis may include other types of cervical lesions, such as squamous metaplasia, reactive changes, or glandular changes. Invasive squamous cell carcinoma of the cervix (when a precancerous lesion invades beyond the basement membrane) should not be ruled out and is the primary concern for this patient.

What Screening Modalities Are Recommended to Detect Cervical Lesions and How Do They Impact Disease Progression?

Cervical cytologic screening was introduced decades ago and is still the most effective cancer prevention test today. For example, cytology screening that is only performed twice in a woman's life can reduce her risk for cervical cancer by 43%.[1] Cytologic testing and HPV co-testing for HPV infection decrease the prevalence and mortality of cervical cancer. Furthermore, regular screening allows for early intervention and reduces progression of disease.

Since cervical SIL is mostly a disease of reproductive-aged women, the American College of Obstetricians and Gynecologists (ACOG) recommends women aged 21 to 29 years have a Pap test every 3 years without HPV testing. Women aged 30 to 65 years should have a Pap test and co-testing for HPV every 5 years.[2]

HPV testing is not recommended for women younger than 30 years because the prevalence of HPV positivity is very high in these women, and the vast majority will completely clear their infections within 1 year.[3] However, for women older than 30 years, liquid-based Pap screening in conjunction with HPV co-testing has a lower false-negative rate and will detect a greater number of patients at risk compared to Pap testing alone.

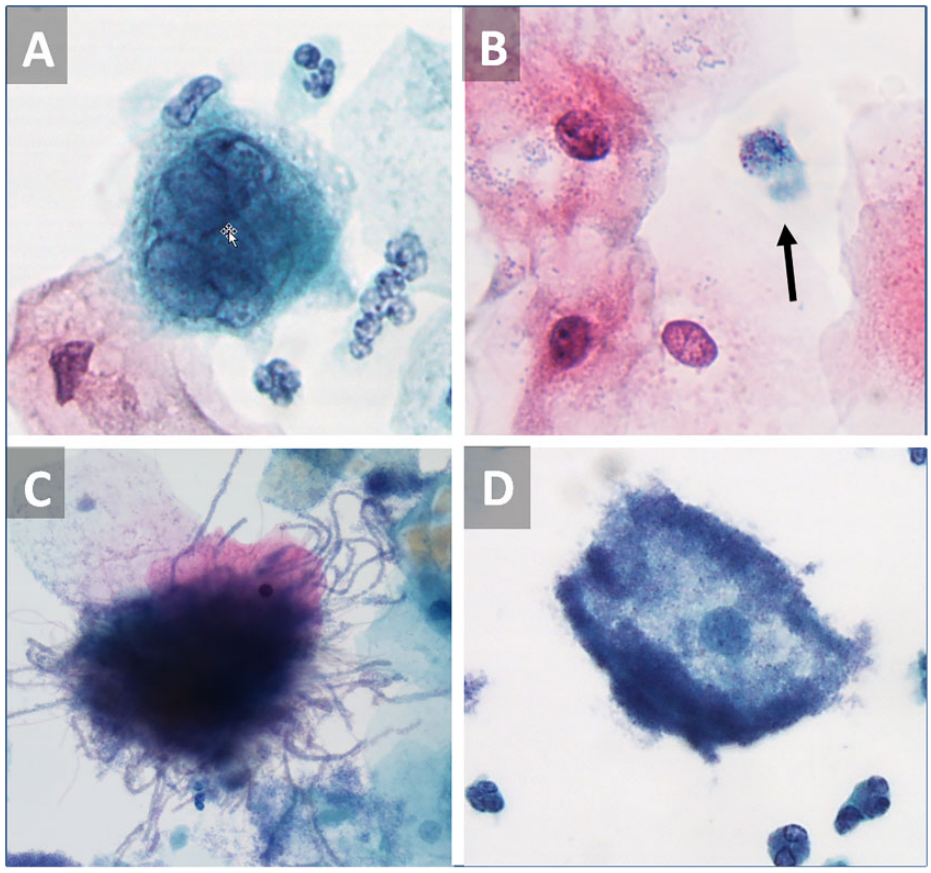

Figure 2. Common infectious findings on Pap smear: (A) herpes simplex virus, (B) trichomonas vaginalis (arrow pointing to trichomonal parasite), (C) actinomyces, (D) Clue cell (indicating a shift in vaginal flora).

In 2014, the ATHENA (Addressing THE Need for Advanced HPV diagnostics) study examined the ability of HPV testing alone to identify women at risk of developing cervical squamous lesions. The study demonstrated that primary screening using only HPV testing can be an effective screening strategy in some patients. Based on data from this study, the Food and Drug Administration (FDA) approved the use of 1 HPV test (Roche Cobas HPV test) for primary cervical cancer screening (without cytology) in women aged 25 years and older.

Although HPV testing may be able to identify the presence of nucleic acids from high-risk HPV types and serial testing can demonstrate persistent infection, Pap testing still has several advantages over HPV testing alone. Since the Pap smear is not designed solely around HPV, it can provide tremendous additional information about the cervical and sexual health of a woman. Although not initially designed for this purpose, the Pap smear can identify numerous infections, including herpes, trichomonas, actinomyces, and bacterial vaginosis (Figure 2). It can even identify the presence of cancer cells from other gynecological sites, such as endometrial carcinoma. Additionally, Pap staining, which is designed to identify the lesions produced by HPV infections, can provide information about how progressive the disease has become whereas HPV testing alone cannot.

Why Is Cervical Cancer, in Particular, a Disease for Which It Is Appropriate to Create a Screening Program?

In 1968, James Wilson published a World Health Organization pamphlet that addressed objective principles which any successful screening program must meet.[4] The principals were primarily not only related to the disease itself but also addressed case identification through testing. In brief, Wilson established that in order for a screening program to be successful, the associated disease must be a public health burden, there should be a pathophysiologic understanding of the disease, there must be a predisease state in which we can identify possible cases, there should be a cost-effective test for the disease and there should be an available treatment for the disease. Cervical cancer, along with our understanding of HPV-related neoplasia and progression to cancer, successfully meets all of these requirements and, therefore, was historically a prime candidate for a screening strategy.[4]

Explain the Pathophysiologic Process That Occurs in the Development of Squamous Intraepithelial Lesion/Cancer: How Is Human Papillomavirus Involved?

The HPV genotypes which have a documented association with squamous lesions and can progress to invasive cancer are termed "high risk." Other "low-risk" genotypes may cause other lesions such as genital warts but do not progress to cancer. Of the high-risk HPV types, genotypes 16 and/or 18 have been identified in the majority of cervical cancers.

The pathogenesis of cervical cancer requires 2 biologically interrelated features: a productive HPV viral infection and an epithelial neoplastic process. According to this model, there is initially an infection with a high-risk type of HPV that persists and progresses to a pathologically defined precursor lesion and ultimately to invasion[3] (Figure 1).

Squamous lesions develop after HPV infected the basal or primitive cells of the immature squamous epithelium through defects or breaks in the skin or mucous membranes. The early region of the HPV genome includes transforming regions E6 and E7 whose corresponding proteins bind to and inhibit the host cell–regulatory proteins, p53 and Rb. This causes unrestricted cell proliferation and blocks cellular apoptosis. Most SIL starts at the squamocolumnar junction of the transformation zone of the cervix. Viral DNA replication occurs mostly in the superficial and intermediate cell layers of the squamous epithelium. As these infected cells move to the epithelial surface, differentiation-specific transcriptional factors from the host cells stimulate the production of viral capsid proteins and subsequently intact virions that produce characteristic cytologic and histologic changes[3] (see Figure 1).

Describe the Natural History of Human Papillomavirus Infections and Its Relation to Neoplasia

Most HPV infections are transient, becoming latent or undergoing immunologic clearance within 1 to 2 years of diagnosis.[1] However, infections with high-risk types of HPV clear more slowly and persistence of infection increases the likelihood of developing high-grade lesions. Prevalence of HPV infection peaks in the late teens to early 20s, while the incidence of cervical cancer in unscreened populations ranges from 35 to 55 years of age. Since HSIL is more common than invasive cervical cancer, this suggests that only a small portion of HSIL progresses to malignancy.[1] We, therefore, understand that although the development of invasive cervical cancer requires persistent infection with high-risk types of HPV, it is not always sufficient to cause cancer. Other associated risk factors include cigarette smoking, long-term use of combined oral contraceptive pills, and immunosuppression.[3]

Describe the Cytopathological Features of Some Common Cervical Infections Which Can be Found on the Pap Stain

Cervical cytology has relatively high specificity for most organisms and can help guide clinical management (see Figure 2).

A. Herpes simplex virus (HSV): The classic features of HSV infections on Pap staining are described as the "three M's of herpes": multinucleation, margination of chromatin, whereby the rim of the individual nuclei appears darker staining than the center, and molding which is seen as each nucleus indenting the neighboring nuclei. With the accumulation of viral particles, the nuclei may develop a "ground glass" appearance.
B. Trichomonas vaginalis: The parasitic organisms are visible with liquid-based preparations. They appear as pear-shaped organisms with an eccentrically located nucleus, eosinophilic cytoplasmic granules, and flagella.
C. Actinomyces: Clumps of woolly filamentous organisms which are usually deeply staining and may demonstrate acute angle branching.
D. Clue cells: Irregularly shaped squamous cells covered with darkly staining coccobacilli. These cells typically indicate a change in the cervical microbiological flora and may be an indication of bacterial vaginosis.

What Systems Are Used to Classify Lesions Identified by Cervical Cytology? How About Classification of Cervical Histopathology?

The Bethesda System (TBS) is used to categorize cytological diagnoses, while the Lower Anogenital Squamous Terminology (LAST) project describes histological findings associated with HPV throughout the anogenital tissues, including the cervix.[5] The Bethesda system utilizes a 2-tiered system of classification (LSIL or HSIL) and previously histopathologists utilized a 3-tiered system (cervical intraepithelial neoplasia [CIN]-I, CIN-II, and CIN-III). Large studies have demonstrated significant diagnostic variation between CIN-II and CIN-III; additionally, CIN-II lesions were found to demonstrate similar rates of progression of disease to CIN-III in some instances. For these reasons, the LAST project has adopted a 2-tiered diagnostic system and both LAST and TBS are in line with one another.[6]

Compare and Contrast Cytopathology and Histopathology in the Images

A. Cytology LSIL:

Cells have enlarged nuclei, about 4 times the size of a normal intermediate cell nucleus. The nuclei are darker (hyperchromatic) with wrinkled irregular nuclear membrane contours. Cells may be multinucleated as seen in the image and the chromatin is finely granular. Areas of clearing around the nucleus (koilocytosis), a hallmark of LSIL, are also seen (Figure 3).

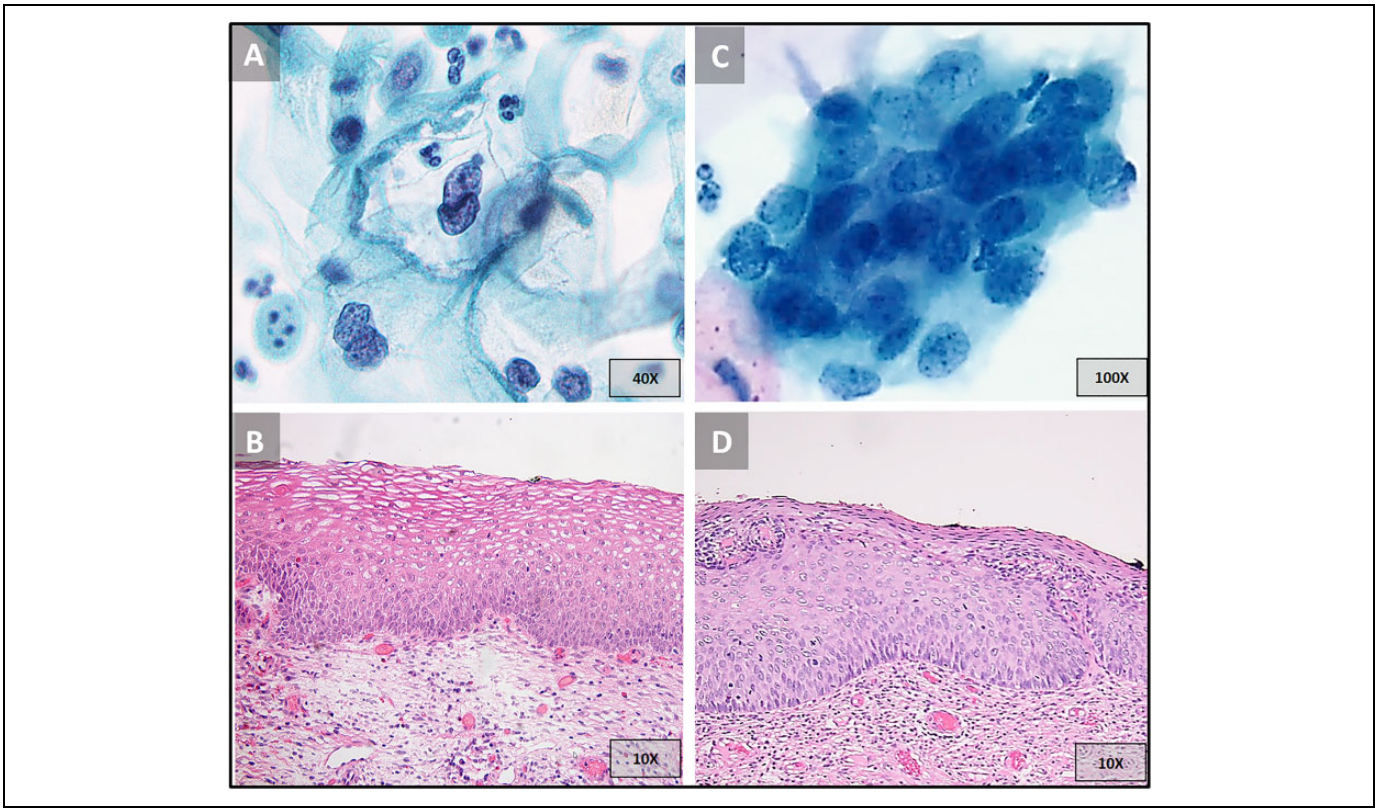

Figure 3. Cytologic and histologic images of low-grade SIL (A, B) and high-grade SIL (C, D). SIL indicates squamous intraepithelial lesion.

B. Histology LSIL (Previously CIN-I):

Nuclei are enlarged and irregularity shaped. There is also darkening of the chromatin (hyperchromasia). Koilocytes with their large vacuoles can be seen in the middle layers, while the superficial layers still resemble a fairly normal basket weave appearance of unaffected epithelium. Overall, there is increased thickness of the epithelium.

C. Cytology HSIL:

The degree of nuclear atypia is increased, such that the nuclei of these cells appear more hyperchromatic and irregular. The amount of cytoplasm decreases as nuclear to cytoplasmic (N:C) ratio increases. The classical features of a mature squamous cell with abundant cytoplasm are no longer seen, and these cells appear less differentiated.

D. Histology HSIL:

Undifferentiated neoplastic cells which no longer resemble the normal squamous cells are present in all layers of the epithelium. The lower layers of the epithelium (basal and parabasal) are thickened, and abnormal mitotic figures are visible. There is nuclear crowding, and cellular variation (pleomorphism) is seen. These areas may appear "bluer" under the microscope because there is less pink cytoplasm. The N:C ratio is high due to scant cytoplasm.

What Is the Recommended Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors? How Should You Proceed Now With More Advanced Disease Present?

The ASCCP *Updated consensus guidelines for managing abnormal cervical cancer screening tests and cancer precursors* outlines the recommendations for managing patients with cervical cytological abnormalities. Although it takes many years for HSIL to progress to invasive cancer, untreated higher grade lesions are also more likely to persist and progress than regress.[3] Therefore, appropriate disease follow-up and management are crucial.

Since our patient now presents with evidence of HSIL on cytology, it is recommended that she undergoes an immediate LEEP or colposcopy with endocervical assessment. Management by ASCCP guidelines differs depending on the colposcopy results. If the biopsy confirms HSIL, either excision or ablation of the "transformation zone" is recommended, followed by co-testing at 12 and 24 months.[1]

What Other Factors Aside From Screening May Alter the Future Burden of This Disease on the Population?

The HPV is an immunologically cleared infection. As such, it was a prime candidate for the development of a multivalent HPV vaccine. Currently, there are 3 FDA–approved HPV vaccines on the

market: Gardasil, Gardasil 9, and Cervarix. The Cervarix vaccine is designed for immunity against HPV 16 and HPV 18, the 2 most common high-risk HPV types that cause about 70% of cervical cancer. Gardasil adds coverage for 2 additional low-risk HPV genotypes (6 and 11) which are the major cause of genital warts. Gardasil 9 extends coverage further to 5 additional high-risk HPV genotypes associated with cervical cancer. These vaccines consist of nonreplicative viral-like particles which provoke an immune response and provide humoral immunologic memory.[7] Currently, several international health-based organizations recommend HPV vaccination be a part of all routine immunization programs. It is important to note that screening following immunization is still required and we have discussed several additional benefits to screening beyond identification of HPV infection.

Describe Some Possible Therapies That Are Being Developed to Treat Human Papillomavirus–Associated Lesions and Cancers

While the initial therapy of squamous lesions is currently complete excision, other novel therapies are currently being evaluated. We have discussed vaccines to prevent infection that are widely available and utilize viral structural proteins. There are currently in development vaccines that help a person's immune system to clear the HPV after infection. Most of these vaccines target HPV oncoproteins E6 and E7.[8] This treatment is anticipated to become clinically available in the near future to decrease the HPV-associated disease burden. Furthermore, research on a pelvic sentinel lymph node biopsy procedure, immunotherapy, and targeted drug therapy is also being conducted.

Teaching Points

- Characteristic cytologic and histologic features, such as koilocytosis, enlarged nuclei, and increased N:C ratio, allow pathologists to diagnose and classify different grades of squamous cervical pathology from low-grade to high-grade squamous lesions and ultimately to carcinoma.
- Classifications based on these features allow one to predict the biologic behavior and malignant potential of these precancerous lesions.
- HPV infection, particularly with high-risk types of HPV, is not only a major risk factor for developing cervical SIL/cancer but also a crucial factor in the pathogenesis of this disease.
- Adequate screening for cervical precancerous pathology may include both cytology Pap and ancillary HPV testing as each method has distinct advantages for the detection of pathologic conditions.
- Cervical disease and its associated diagnostic testing are a paradigmatic model of disease screening and intervention and remain one of the most successful screening programs ever devised.
- Several organizations, including the ACOG and the ASCCP, regularly publish guidelines related to screening and management of the cervical cancer.

Declaration of Conflicting Interests

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Educational Case: Medullary Thyroid Carcinoma

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, cytology diagnostic certainty, endocrine, endocrine neoplasms, fine needle aspiration cytology, medullary thyroid carcinoma

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Primary Objective

EN5.2: Medullary Thyroid Carcinoma. Describe the molecular basis and clinicopathologic features of medullary thyroid carcinoma.

Competency 2: Organ System Pathology; Topic EN: Endocrine; Learning Goal 5: Endocrine Neoplasms.

Secondary Objective

CYP1.2: Categorizing Diagnostic Certainty. Compare and contrast the degree of diagnostic certainty applied to general categorization in cytologic diagnosis.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic CYP: Cytopathology; Learning Goal 1: Cytologic Diagnosis.

Patient Presentation

A 52-year-old Caucasian male presents to family medicine with an irregular 4-cm palpable nodule in the mid right thyroid lobe. He has no significant past medical history other than occasional diarrhea. Complete head and neck examination reveals no additional palpable nodules in the thyroid gland and no palpable adenopathy. The differential diagnosis for a palpable thyroid nodule includes a variety of benign and malignant entities, including colloid nodule, nodular hyperplasia, follicular thyroid adenoma, follicular thyroid carcinoma, papillary thyroid carcinoma (PTC), medullary thyroid carcinoma (MTC), anaplastic thyroid carcinoma, and lymphoma. The patient is referred to the lab for pathologist to perform fine needle aspiration (FNA) cytology of the nodule.

Diagnostic Findings, Part 1

The pathologist performs 3 FNA passes into the nodule under direct guidance using 25-gauge needles without suction, and the initial smears show adequate cellularity (Figure 1). Additional passes are not performed for cell block preparation. Using The Bethesda System for Reporting Thyroid Cytology, the pathologist finalizes the report as Bethesda category V, suspicious for malignancy and MTC. The cytology findings are shown in Figures 1 and 2 and compared to the more common PTC in Figure 3. The patient is referred to endocrinology for further evaluation.

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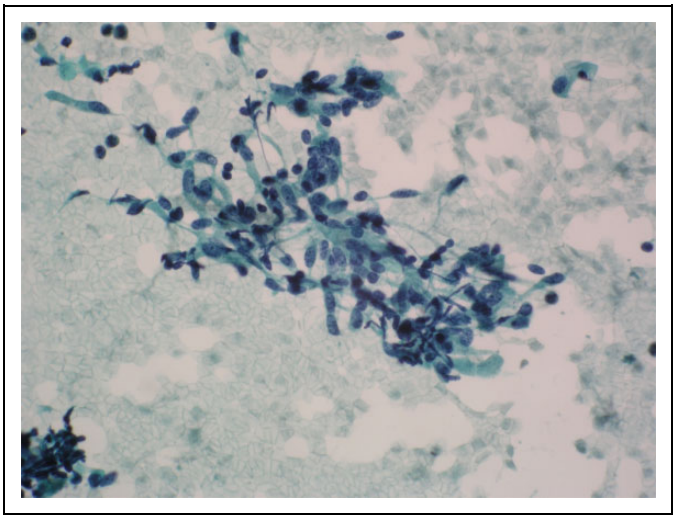

Figure 1. Papanicolaou stain at ×200 of the initial FNA smear showing background red blood cells, scant colloid, and a mixed population of neoplastic cells showing epithelioid and spindle cell morphology. Nuclear chromatin shows a "'salt and pepper" granularity and lacks features of papillary carcinoma (Figure 3), and the cell cytoplasm is somewhat granular. FNA indicates fine needle aspiration cytology.

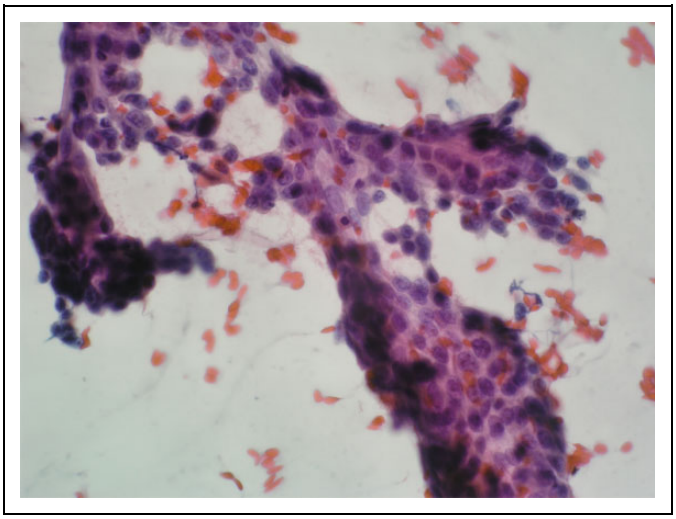

Figure 3. Papanicolaou stain of PTC for comparison with the patients with FNA cytology. Papillary thyroid carcinoma shows nongranular chromatin, nuclear grooves, small peripheral nucleoli, and occasional intranuclear pseudo-inclusions. Papillary-shaped irregular branching groups are also present. FNA indicates fine needle aspiration cytology; PTC, papillary thyroid carcinoma.

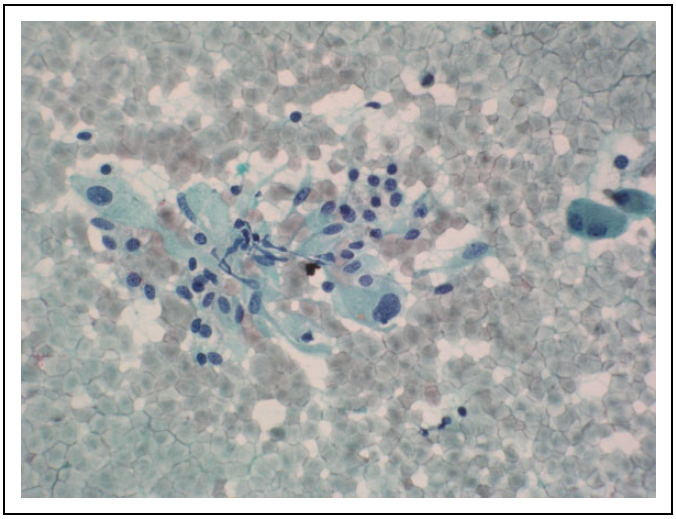

Figure 2. Papanicolaou stain at ×400 highlighting random nuclear atypia often seen in neuroendocrine neoplasia, as well as the granular cytoplasm and fine-to-coarse nuclear chromatin of medullary thyroid carcinoma.

Questions/Discussion Points, Part 1

Categorizing Diagnostic Certainty: Based on the Pathologist's Interpretation of the FNA, How Statistically Likely is the Patient to Harbor a Malignant Neoplasm and What is the Uncertainty of the Diagnosis?

The major categories used in diagnostic cytopathology include unsatisfactory for diagnosis, negative for malignancy, atypical cells present, suspicious for malignancy, and positive for malignancy. Each category carries an implied degree of certainty with regard to the pathology present. Diagnostic modifiers are also used in surgical pathology to suggest degrees of uncertainty, including "cannot rule out," "suggestive of," "consistent with," and "diagnostic of," in increasing order of certainty.[1] The issue of uncertainty in anatomic pathology diagnosis is highlighted by the presence of both interobserver (2 observers arriving at a different diagnosis on the same case) and intraobserver (the same observer arriving at different diagnoses on the same case at different times) diagnostic variation.[2]

Interinstitutional review of 777 patient specimens revealed a diagnostic difference in 71 specimens on review at the second institution. In 45 of the 71 discrepant specimens, the change in diagnosis led to altered therapy. The discordant diagnoses were significantly more common in cytology specimens (21%) than surgical specimens (7.8%), suggesting that cytologic diagnosis was more prone to uncertainty than histologic diagnosis.[3]

Historically, cytopathologists at different institutions have utilized somewhat different diagnostic terminology when reporting results of thyroid FNA. To address the variety of reporting systems and the resulting inherent confusion, the National Cancer Institute (NCI) hosted the NCI Thyroid FNA State of the Science Conference. The conference conclusions led to the publication of the Bethesda System for Reporting Thyroid Cytology,[4] which is now in wide use. Similar issues led to publication of the Paris System for Reporting Urinary Cytology.[5]

The Bethesda System for Reporting Thyroid Cytology[4] contains 6 general diagnostic categories, each with a specific given risk of underlying malignancy as shown in Table 1. The least amount of uncertainty is associated with the benign and malignant categories as these have the narrowest range for underlying malignancy. The greatest degree of uncertainty lies with the atypical category which shows the widest range for underlying

Table 1. Major Diagnostic Categories of The Bethesda System for Reporting Thyroid Cytology and the Associated Risk of Malignancy.

Diagnostic Category	Underlying Risk of Malignancy (%)
ND/unsatisfactory (I)	1-4
Benign (II)	0-3
AUS/FLUS (III)	5-15
FN/SFN (IV)	15-30
Suspicious for malignancy (V)	60-75
Malignant (VI)	97-99

Abbreviations: AUS, atypia of uncertain significance; FLUS, follicular lesion of uncertain significance; FN, follicular neoplasm; ND, nondiagnostic; SFN, suspicious for follicular neoplasm.

Table 2. Diagnostic Categories of The Paris System for Reporting Urinary Cytology and the Associated Risk of Malignancy.

Diagnostic Category	Underlying Risk of Malignancy (%)
Unsatisfactory	<5-10
Negative for HGUC	0-10
Atypical urothelial cells	8-35
Suspicious for HGUC	50-90
Low-grade urothelial neoplasm	~10
Positive for HGUC	>90
Positive for other malignancy	>90

Abbreviation: HGUC, high-grade urothelial carcinoma.

malignancy, and the suspicious category being between atypical and benign/malignant in terms of uncertainty. Thyroid FNA is somewhat unique in having 2 suspicious categories. Suspicious for follicular neoplasm less commonly has an underlying malignancy when compared to the suspicious for malignancy category, as the majority of follicular neoplasms are benign adenomas, rather than follicular carcinomas.

Similar uncertainty is seen in other types of cytology specimens, such as urine cytology using The Paris System for Reporting.[5] The risk of underlying malignancy in urine cytology based on The Paris System reporting is shown in Table 2. The wider the range for underlying malignancy, the greater the uncertainty for that diagnostic category.

In general, both benign and malignant cytologic diagnostic categories have the least associated uncertainty, and the most significant uncertainty is in the atypical category, with the suspicious category intermediate for the associated degree of uncertainty. Currently available molecular tests are available for use on ambiguous thyroid FNAs, to identify malignancy-associated genetic changes. These serve to decrease the broad diagnostic uncertainty in the atypical follicular cells of uncertain significance category and help direct treatment decisions (surgery vs continued clinical observation).

Diagnostic Findings, Part 2

The endocrinologist does a typical thyroid endocrine workup and finds that the patient is euthyroid and has a normal calcium.

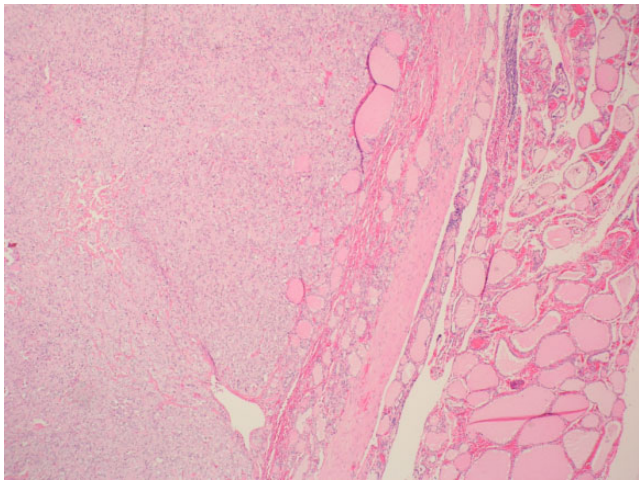

Figure 4. Hematoxylin and eosin stained section of the tumor thyroid interface at ×40 showing a well-circumscribed cellular neoplasm on the left without follicular or papillary architecture. The tumor was incompletely encapsulated, and entrapped benign follicles are seen at the periphery. The adjacent thyroid tissue showed no evidence of C-cell hyperplasia and contains medium-to-large colloid-filled follicles on the right.

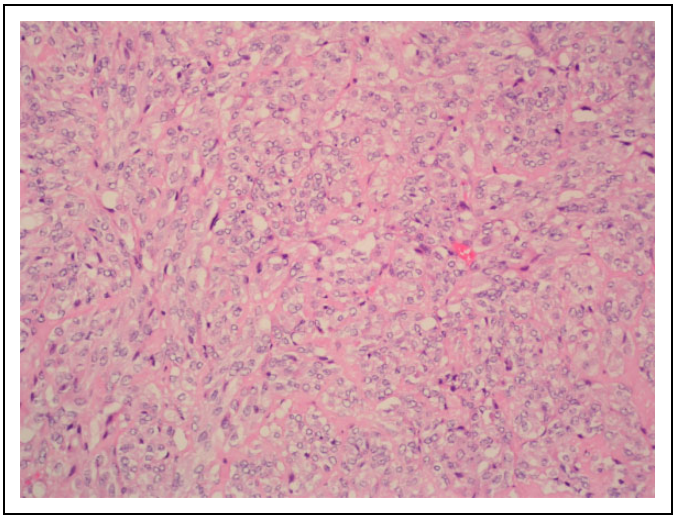

Figure 5. Hematoxylin and eosin stained section of tumor at ×200 showing mixed epithelioid and spindled morphology with only vague nesting of tumor cells and a majority diffuse growth pattern. Amyloid was not present.

Because of the suspicion of MTC on the FNA, he also performs a serum calcitonin that comes back as 5679 pg/mL (normal <10 pg/mL). The patient is referred to otolaryngology and a total thyroidectomy and central and bilateral node dissection is performed. The final pathology shows a 3.9-cm medullary carcinoma (Figures 4-6) confined to the thyroid gland with 3 of 6 central nodes microscopically involved and none of 13 right and 1 of 11 left neck nodes involved by medullary carcinoma. The pathologic stage is reported as pT2, pN1a, pM-not applicable, or stage group III.

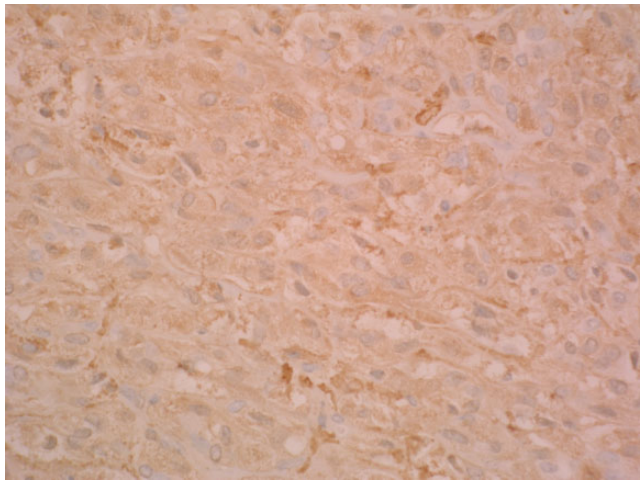

Figure 6. Immunochemistry of tumor for calcitonin ×400 showing diffuse granular cytoplasmic staining.

Questions/Discussion Points, Part 2

What Clinicopathologic Features are Common in Both Sporadic and Inherited Medullary Thyroid Carcinoma?

Medullary thyroid carcinoma is a primary tumor of the thyroid gland which shows differentiation along the lines of thyroid parafollicular C cells.[6-8] Medullary thyroid carcinoma typically secretes calcitonin, although nonsecretory tumors occur rarely. Serum calcitonin reflects quantity of tumor present, except in nonsecreting patients. Medullary thyroid carcinoma is almost always carcinoembryonic antigen (CEA) positive, and in noncalcitonin-secreting tumors, serum CEA levels can be followed, similar to calcitonin levels in secreting tumors to assess disease burden and therapeutic response. Even though elevated calcitonin levels are present, serum calcium is not typically decreased below normal levels. Medullary thyroid carcinoma tumors sometimes secrete other hormones, such as adrenal corticotropic hormone, serotonin, and vasoactive intestinal peptide (VIP), which can result in a paraneoplastic presentation such as diarrhea if VIP secretion occurs. The VIP levels were not measured in this patient, and it is not clear whether his intermittent diarrhea was related to the MTC. Medullary thyroid carcinomas are relatively uncommon tumors accounting for less than 2% to 3% of thyroid neoplasia.

Medullary thyroid carcinoma can present as a sporadic tumor or as part of an inherited tumor syndrome. The histology of MTC is quite variable, but in general is not distinct for sporadic or inherited cases. A mixture of spindled and epithelioid cells is common, and plasmacytoid morphology is often seen. Neuroendocrine features include finely granular cytoplasm due to variable presence of neurosecretory granules. The chromatin is mixed fine and coarse and classically described as "salt and pepper" chromatin which is commonly seen in neuroendocrine tumors. Cells can be arranged in sheets, nested aggregates, trabeculae, or even follicles, and mitotic figures tend to be sparse. These features of MTC contrast with the more common PTC (Figure 3). Nuclear features of PTC include pale nongranular nuclear chromatin, nuclear grooves, nuclear pseudoinclusions, and small peripheral nucleoli. Amyloid deposition is commonly present in up to 90% of cases, but was absent in this particular case, and is composed of calcitonin peptides. Immunochemistry shows positive granular cytoplasmic staining for calcitonin in the tumor cells and diffusely stains the amyloid deposits. Immunochemistry is also positive for other neuroendocrine markers, such as chromogranin and synaptophysin. Cytologic atypia ranges from minimal, to focal, to widespread.

Describe the Features Unique to Sporadic Medullary Thyroid Carcinoma

Medullary thyroid carcinoma occurs as sporadic disease in 70% of cases, and the sporadic cases present typically as a neck mass, as in this case, but clinical findings may also include dysphagia and/or hoarseness. When MTC presents as a neck mass, nodal involvement is relatively frequent (~70%) and non-nodal metastasis (10%) also occurs. Sporadic cases show a slight female predominance and are seen predominantly in the fifth and sixth decades. These are usually unilateral and unifocal tumors of the thyroid. Unlike PTC, ionizing radiation exposure does not seem to be etiologically involved in sporadic MTC.

Describe the Features Unique to Inherited Medullary Thyroid Carcinoma

Familial cases occur as part of inherited syndromes in 30% of cases (multiple endocrine neoplasia type 2A [MEN-2A] or MEN-2B or familial medullary thyroid carcinoma [FMTC]) and are often associated with other endocrine neoplasms. Medullary thyroid carcinoma in this setting may present either as a result of endocrine disease in other organs or with symptoms in the neck. Familial/inherited cases present at younger ages than do sporadic cases. Medullary thyroid carcinoma in the setting of MEN-2B more commonly metastasizes than what is seen in MEN-2A, FMTC, or sporadic disease. Bilateral thyroid involvement and multifocal disease are more common in inherited MTC than in sporadic disease. Penetrance of medullary thyroid cancer development is age and mutation dependent; however, MTC inevitably develops in MEN-2 with *RET* mutations, and early total thyroidectomy is preventative. Early onset is typical in MEN-2B with later onset in MEN-2A. Thyroid tissue outside the tumor in inherited cases typically shows background C cell hyperplasia.

Describe the Molecular Basis of Sporadic Medullary Thyroid Carcinoma

Activating somatic point mutations of the *RET* proto-oncogene are noted in sporadic medullary carcinoma in approximately 40% to 60% of cases. The most frequently seen mutation in

sporadic cases is the M918T mutation in exon 16. Interestingly, this is also the same mutation as the germline mutation in the vast majority of MEN-2B patients. *RAS* mutations are also seen in some sporadic cases, usually those that are *RET* mutation negative. Thus, in sporadic disease, *RAS* and *RET* mutations commonly show mutual exclusion.

Describe the Molecular Basis of Inherited Medullary Thyroid Carcinoma

Germline mutation of the *RET* proto-oncogene with gain of function is the underlying feature in inherited MTC, as seen in MEN-2A, MEN-2B, and FMTC (a variant of MEN-2A). The *RET* proto-oncogene codes for a receptor tyrosine kinase that binds glial-derived neurotrophic factor and similar ligands. Ligand binding to receptor leads to intracellular growth signals as well as signals for differentiation. Various specific *RET* mutations occur in MEN-2A, and coexisting parathyroid hyperplasia and pheochromocytoma are characteristic. The specific *RET* mutations in MEN-2B are associated with pheochromocytoma as well; however, the hyperparathyroidism is absent.

Teaching Points

- Major cytologic diagnostic categories (nondiagnostic, benign, suspicious, and malignant) each carry an associated risk of underlying malignancy and uncertainty, which have been published for various types of specimens.
- Cytologic diagnostic categories of benign and malignant have the least amount of associated diagnostic uncertainty and the atypical category the highest.
- Medullary thyroid carcinoma is a neuroendocrine tumor showing C-cell differentiation.
- Medullary thyroid carcinoma is immunochemically positive for calcitonin (which is elevated in serum, except in rare nonsecreting cases), chromogranin, synaptophysin, and CEA.
- Medullary thyroid carcinoma can be followed clinically with serum calcitonin or CEA, and CEA is helpful in calcitonin nonsecreting cases.
- Occasionally, MTCs secrete other hormones and may have paraneoplastic presentations, for example, VIP—diarrhea.
- Medullary thyroid carcinoma can be sporadic or inherited.
- Sporadic and inherited MTCs have the same histologic spectrum with amyloid deposition, sporadic disease typically being unilateral and unifocal and inherited disease more likely to be bilateral and multifocal.
- Inherited MTC shows C-cell hyperplasia in the nonneoplastic thyroid tissue.
- Specific genetic and molecular mechanisms underlie both sporadic and inherited medullary thyroid cancer, with the *RET* gene being most frequently involved.
- The inevitable development of medullary thyroid cancer associated with MEN-2 can be prevented by early prophylactic total thyroidectomy.

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Subarachnoid Hemorrhage Related to Ruptured Berry Aneurysm

Sarah Meyers, MD[1]

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, diagnostic medicine, therapeutic pathology, central nervous system, berry aneurysm, death certificate, death investigation, intracranial hemorrhage, subarachnoid hemorrhage

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Primary Objective

Objective NSC7.3: Cranial Hemorrhage. Compare and contrast the etiologies and clinical presentations of epidural, subdural, subarachnoid, basal ganglionic, and lobar hemorrhages.

Competency 2: Organ System Pathology; Topic NSC: Nervous System–Central Nervous System; Learning Goal 7: Ischemia of the Brain.

Secondary Objective

Objective AU2.2: Components of the Death Certificate. Discuss the key components of the death certificate; differences among immediate, intermediate, and underlying (proximate) cause of death based on disease process; and the role of mechanisms of death on a death certificate.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic AU: Autopsy; Learning Goal 2: Death Certificate.

Clinical Case

A 47-year-old female with a medical history of migraine headaches, with migraine pain controlled by codeine, is found dead on the floor of her secured residence. No outward signs of trauma or foul play were identified at the scene of death. Given her relatively young age and minimal medical history, an autopsy was requested and performed by the county medical examiner. Following resection of the skull and dura, the following intracranial finding was identified (Figure 1). The pathologist reports that this collection cannot be wiped from the surface of the brain. The hemorrhage appeared to be concentrated at the base of the brain. The circle of Willis was dissected and showed the abnormality identified by the arrow (Figure 2).

Questions/Discussion Points

Given the photograph and the description, what is the name of the finding featured in Figure 1? How would the gross description be different for other types of intracranial hemorrhage? If a CT was performed for this entity, how might the findings be reported?

The photograph shows subarachnoid hemorrhage. A subarachnoid hemorrhage is confined by the arachnoid layer and

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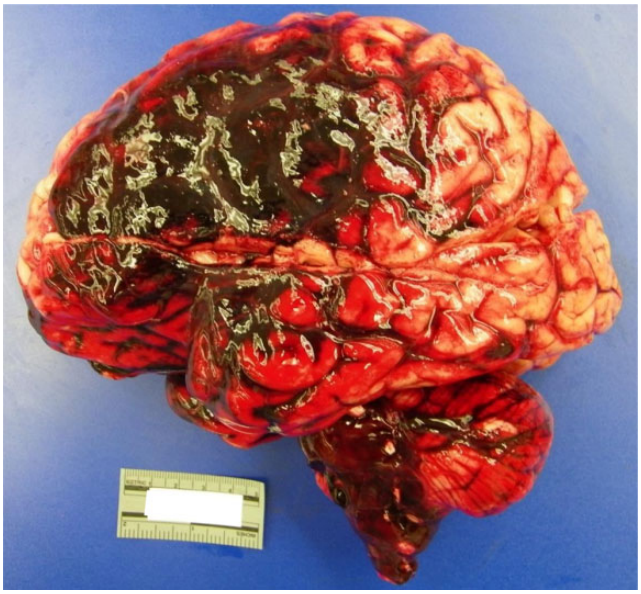

Figure 1. Brain with subarachnoid hemorrhage.

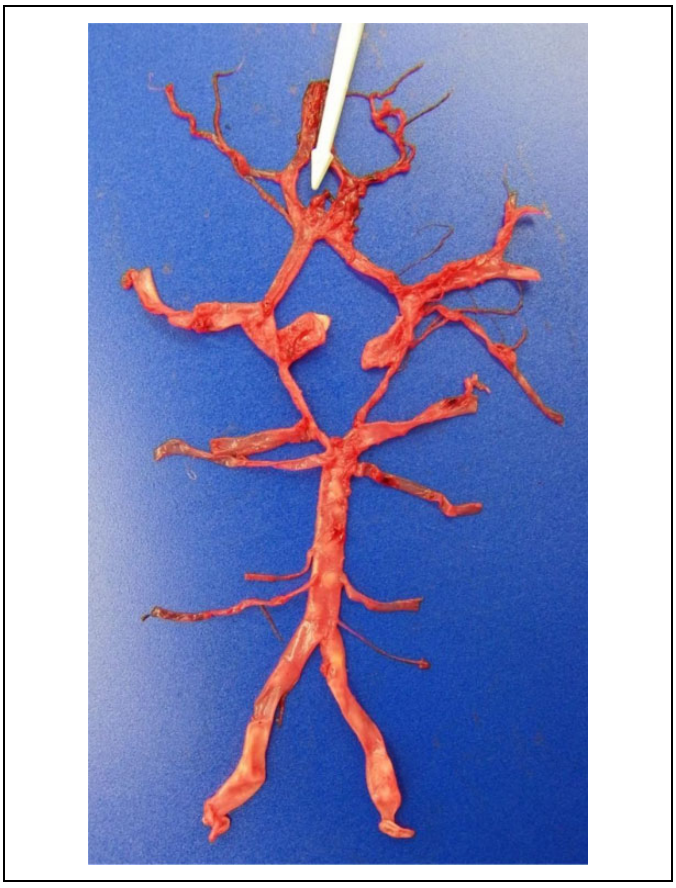

Figure 2. Dissected circle of Willis demonstrating ruptured berry aneurysm at the bifurcation of the anterior communicating artery and the anterior cerebral artery.

cannot be wiped or rinsed away from the brain. Radiographically, subarachnoid hemorrhage would be demonstrated by thin layers of blood overlying structures, such as the sylvian fissure, intrahemispheric fissure, or basal cisterns. Subdural hemorrhage consists of blood filling the potential space beneath the dura, but outside the subarachnoid space. At gross inspection, subdural blood would be able to be wiped or washed away from the surface of the brain and not retained within the cell layer of the subarachnoid space. CT imaging generally shows a crescentic shaped area of hemorrhage outside the brain parenchyma, beneath the skull. Intraparenchymal hemorrhages, such as those related to hypertension or tumors, would be centered within and usually surrounded by brain parenchyma; however, these areas of hemorrhage may expand to communicate with the subarachnoid, subdural, or intraventricular space. CT imaging of intraparenchymal hemorrhage demonstrates blood within the brain itself.

What is the differential diagnosis for the etiology of the finding demonstrated in Figure 1?

Ruptured berry (saccular) aneurysm, trauma, ruptured arteriovenous malformation, extension of intraparenchymal hemorrhage, hematologic disorders, and coagulopathies.[1] Of these entities, the most common cause of clinically significant subarachnoid hemorrhage is due to a ruptured berry aneurysm.[1]

What is the cause of the hemorrhage based on the finding in Figure 2?

Ruptured berry (saccular) aneurysm.

What are the major complications associated with these autopsy findings?

Statistics vary, but up to 50% of patients die within 1 month of an intracerebral aneurysmal rupture and hemorrhage.[1] Similar to this patient, at least 10% of patients die prior to hospitalization for the first bleed.[1] If a patient survives, major morbidity manifests as delayed ischemic complications related to vasospasm, rebleeding, seizures, hydrocephalus, and hyponatremia.[1]

Acting as the medical examiner, please list the cause (immediate and underlying) and manner of death.

The cause of death is the injury or disease process that resulted in a patient's death. Manner of death is defined by public health parameters and is a selection of natural, accident, suicide, homicide, or undetermined. A death certificate should tell the whole story of a patient's history and should work backward from the underlying cause of death to the immediate cause of death. Care should be taken to ensure that the death certificate is specific, concise, and avoids nonspecific mechanisms of death that are universal to all deaths, such as the phrase cardiorespiratory arrest. As such, the first disease process that

occurred in this patient's case was the rupture of the berry aneurysm leading to the subarachnoid hemorrhage. Both of these processes are natural diseases; therefore, the death certificate should be completed as follows:

Cause of death: Subarachnoid hemorrhage (immediate cause)
Due To: Ruptured berry aneurysm (underlying cause)
Manner of Death: Natural

Teaching Points

- Subarachnoid hemorrhage is demonstrated grossly by a layer of blood confined within the subarachnoid space.
- The differential diagnosis for subarachnoid hemorrhage includes a ruptured berry aneurysm, trauma, ruptured arteriovenous malformation, extension of intraparenchymal hemorrhage, hematologic disorders, and coagulopathies.
- Ruptured berry aneurysms have high morbidity and mortality related to short- and long-term complications related to subarachnoid hemorrhage.
- In completing a death certificate, the cause of death should be ascribed to the underlying disease or injury that set the sequence of events in motion to result in the immediate cause of death.

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