Bryan H. Schmitt
Editor

Atlas of Infectious Disease Pathology

Springer

Atlas of Anatomic Pathology

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Liang Cheng

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Atlas of Anatomic Pathology
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To my wife, Ingrid, who has been there from the beginning. Thank you for all of your love and support.

Series Preface

One Picture Is Worth Ten Thousand Words
— Frederick Barnard, 1927

Remarkable progress has been made in anatomic and surgical pathology during the last 10 years. The ability of surgical pathologists to reach a definite diagnosis is now enhanced by immunohistochemical and molecular techniques. Many new clinically important histopathologic entities and variants have been described using these techniques. Established diagnostic entities are more fully defined for virtually every organ system. The emergence of personalized medicine has also created a paradigm shift in surgical pathology. Both promptness and precision are required of modern pathologists. Newer diagnostic tests in anatomic pathology, however, cannot benefit the patient unless the pathologist recognizes the lesion and requests the necessary special studies. An up-to-date atlas encompassing the full spectrum of benign and malignant lesions, their variants, and evidence-based diagnostic criteria for each organ system is needed. This atlas is not intended as a comprehensive source of detailed clinical information concerning the entities shown. Clinical and therapeutic guidelines are served admirably by a large number of excellent textbooks. This atlas, however, is intended as a "first knowledge base" in the quest for definitive and efficient diagnosis of both usual and unusual diseases.

The *Atlas of Anatomic Pathology* is presented to the reader as a quick reference guide for diagnosis and classification of benign, congenital, inflammatory, nonneoplastic, and neoplastic lesions organized by organ systems. Normal and variations of "normal" histology are illustrated for each organ. The atlas focuses on visual diagnostic criteria and differential diagnosis. The organization is intended to provide quick access to images and confirmatory tests for each specific organ or site. The atlas adopts the well-known and widely accepted terminology, nomenclature, classification schemes, and staging algorithms.

This book series is intended chiefly for use by pathologists in training and practicing surgical pathologists in their daily practice. It is also a useful resource for medical students, cytotechnologists, pathologist assistants, and other medical professionals with special interest in anatomic pathology. We hope that our trainees, students, and readers at all levels of expertise will learn, understand, and gain insight into the pathophysiology of disease processes through this

comprehensive resource. Macroscopic and histological images are aesthetically pleasing in many ways. We hope that the new series will serve as a virtual pathology museum for the edification of our readers.

Indianapolis, IN, USA Liang Cheng

Preface

Infectious disease pathology is a wide encompassing special interest within anatomic pathology, aided by various ancillary testing methods that often fall into the clinical/molecular microbiology realm. Infectious agents can be encountered in any subspecialty of pathology, and while large academic practices may confront them more frequently, smaller community practices are certainly not exempt. While many wonderful general and subspecialty volumes have been written on the subject, the aim of this publication is to provide primarily image-based educational content, geared toward the most frequently encountered infectious entities. It is my hope that this volume will prove to be an easy-to-use reference guide for daily anatomic pathology sign-out in a wide variety of practice settings as well as an educational collection for those interested in learning more about the histopathological manifestations of various infections.

The focus of the images will be on the hematoxylin and eosin (H&E) stained appearances of infectious agents and will highlight common special stains that can be used to aid in diagnoses. Where appropriate, commentary regarding additional testing such as immunohistochemistry and molecular-based testing is supplied. The atlas is organized primarily by pathogen type, followed by a discussion of the various manifestations that may occur in individual organ systems.

As infectious disease pathology is not an emphasis of a typical residency or fellowship curriculum, those pursuing advanced education must often seek the experience of others. As such, I would especially like to thank Dr. Bobbi Pritt for being instrumental in furthering my interest in the subject during my microbiology fellowship training at Mayo Clinic and beyond. I would also like to thank my colleagues Dr. Ryan F. Relich, Dr. Thomas E. Davis, and Dr. James W. Smith from the Indiana University School of Medicine for their insights and access to their extensive archival material. Special thanks also to Lee Klein, senior editor at Springer, for keeping me (mostly) on track during the year and a half development and writing process. I greatly appreciate the assistance. Lastly, I need to thank my wonderful wife, Ingrid, for putting up with the late nights and lost weekends and for her support not only on this project but over my entire career.

For the readers, I hope you enjoy the atlas and that it is a valuable contribution to your medical knowledge.

Indianapolis, IN, USA Bryan H. Schmitt

Contents

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An Introduction to Infectious Disease Pathology

1

Bryan H. Schmitt

Infectious diseases may be encountered in every subspecialty of pathology and can often present difficulties in identification and proper diagnosis. Most anatomic pathology microscopes and workstations are geared toward generally low-magnification diagnoses based primarily on patterns of tissue growth or inflammation. The microscopic diagnosis of many infectious diseases, however, requires much higher magnification, preferably up to at least 1000× total. Therefore, as the initial chapter in this atlas, we will first suggest some basic concepts to help achieve your optimal approach for high-magnification histologic and cytologic microscopy. Readers are of course encouraged to adapt these suggestions to their own practices as they see fit.

1.1 Microscope Setup

Although the setup of microscope objectives is largely a matter of personal preference, the pathologist or clinical microbiologist dealing with frequent infectious disease cases does benefit from proper positioning of oil immersion objectives in particular in order to avoid exposing low-lying objectives (such as a typical 40×) to the oil on the slide. While most surgical pathologists would prefer a 2× scanning objective for daily anatomic pathology work, the author has substituted a 60× "high and dry" objective because this provides additional magnification above a typical 40× without the need for oil immersion.

A stage clip, while eschewed by most anatomic pathologists, is essential here for fine adjustment of the viewing field, especially at higher magnifications. A stage

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Fig. 1.1 Example image of a microscope nosepiece or "turret" with a 50× oil objective (*blue band*) installed adjacent to a 10× dry objective. This setup allows for switching back and forth between higher magnification oil immersion objectives and lower magnification dry objectives appropriate for scanning without running the risk of exposing non-oil objectives to oil

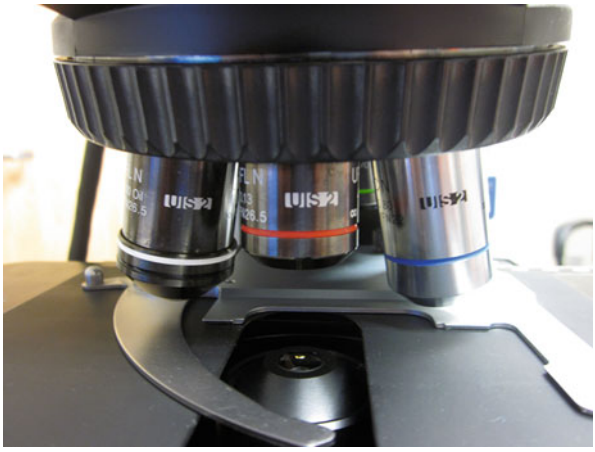

Fig. 1.2 Opposite side of the turret. Note the 4× objective installed adjacent to the 100× oil objective. The author has also opted for a 60× dry objective seen here, which could be swapped out for a 2× scanning objective depending on user preference and mechanics of the microscope. Importantly, the objectives adjacent to the oil immersion objectives are both of a shorter length so as to not allow for submersion into oil, but are also of lower magnification to allow for low power scanning on either side of the higher magnification objectives

clip is also very helpful when taking images for publication, obtaining remote second opinions, or sharing with colleagues.

Several of the microorganisms that will be discussed have components that are birefringent when observed under polarized light. If your microscope setup does not have integrated polarizing capabilities, several low-cost options for external filters are available. Additionally, as the size of microorganisms is often diagnostically helpful, access to a properly calibrated ocular micrometer is very important (Figs. 1.1, 1.2 and 1.3).

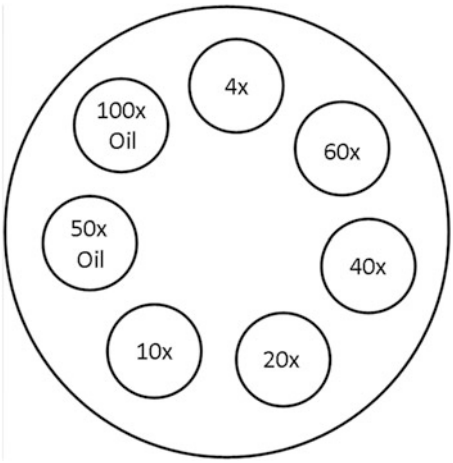

Fig. 1.3 Example layout for a seven objective turret viewed from the stage up. This setup allows for quick switching between high and low magnification objectives, while keeping distance between oil and longer, dry objectives

1.2 Caveats Regarding Histologic Sectioning and the Appearance of Microorganisms

Since histopathology involves sectioning through three-dimensional objects in a flat plane, the appearance of tissues and even cells is significantly altered, depending on orientation. This problem is no more pronounced than in infectious disease cases in which infectious agents, such as parasites, are often comparatively large and folded, resulting in multiple cross-sections through single or multiple organisms; this produces difficulties in reconstructing what is seen under the microscope versus most fine-tuned and ideal images seen in publications or online. While this atlas makes an effort to provide ideal images, "real-world" images are also included to reflect what is more likely to be encountered in clinical practice.

Also of note is that most infectious agents are living organisms, and as such appearances may change depending on the environment, exposure to antimicrobials, or other factors. A good example illustrating this point is found in filamentous fungi, in which the classic "acute angle branching" such as that described in *Aspergillus* species culture specimens may be disrupted. In many cases, this classically described appearance may not be perfectly maintained in histologic sectioning because the organisms grow through different environments, as well as into and around tissues or around themselves. Therefore examination of multiple sections to achieve an overall "consensus" in organism appearance is often required to come to a probable differential diagnosis, with culture results required for a definitive diagnosis (Figs. 1.4, 1.5 and 1.6).

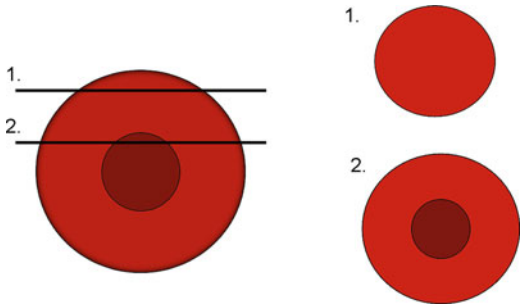

Fig. 1.4 In histopathology, three-dimensional objects are cut along a two dimensional plane. In this simple example, a cell cut along the top, as in plane 1, will only demonstrate cytoplasm, however when cut in plane 2, it will demonstrate the nucleus

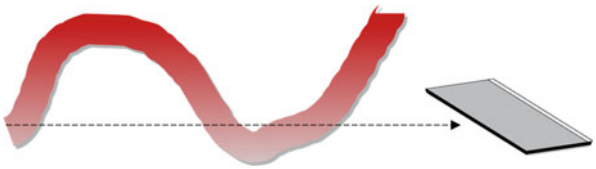

Fig. 1.5 Taking this concept one step further, you can see that if a large organism, such as a worm, were cut in perfect coronal or sagittal section, the overall appearance of the organism as a worm would be maintained, however, we are much more likely to receive cuts in an off-plane, such as the facing of the cartoon microtome blade in this illustration

Fig. 1.6 The end result of the illustration in Fig. 1.5, may therefore end up looking like something more akin to what is seen here, with apparently differently sized and shaped sections as well as evidence of internal structures (*dark red dots*) in some sections and not others

1.3 Special Stains and Immunohistochemistry

Many infectious agents, particularly those of larger size, can be easily visualized using hematoxylin and eosin (H&E) staining alone. Often, however, inflammatory patterns are seen that are suggestive of an infectious process without showing readily identifiable organisms. In these cases, the use of special stains may be necessary to provide a diagnosis.

While evidence of bacterial processes can be suggested by an abundance of acute inflammatory cells or even in some cases visualized by clumps of bacteria, a tissue Gram stain may be helpful in delineating the nature of the infection. The most popular tissue Gram stains are Brown and Hopps and Brown and Brenn. Brown and Hopps stains are traditionally thought to more reliably stain Gram-negative bacteria their intended red color, whereas Brown and Brenn stains are thought to more reliably stain Gram-positive bacteria their intended blue color. Regardless, it is unlikely that most laboratories maintain access to both stains, and there are