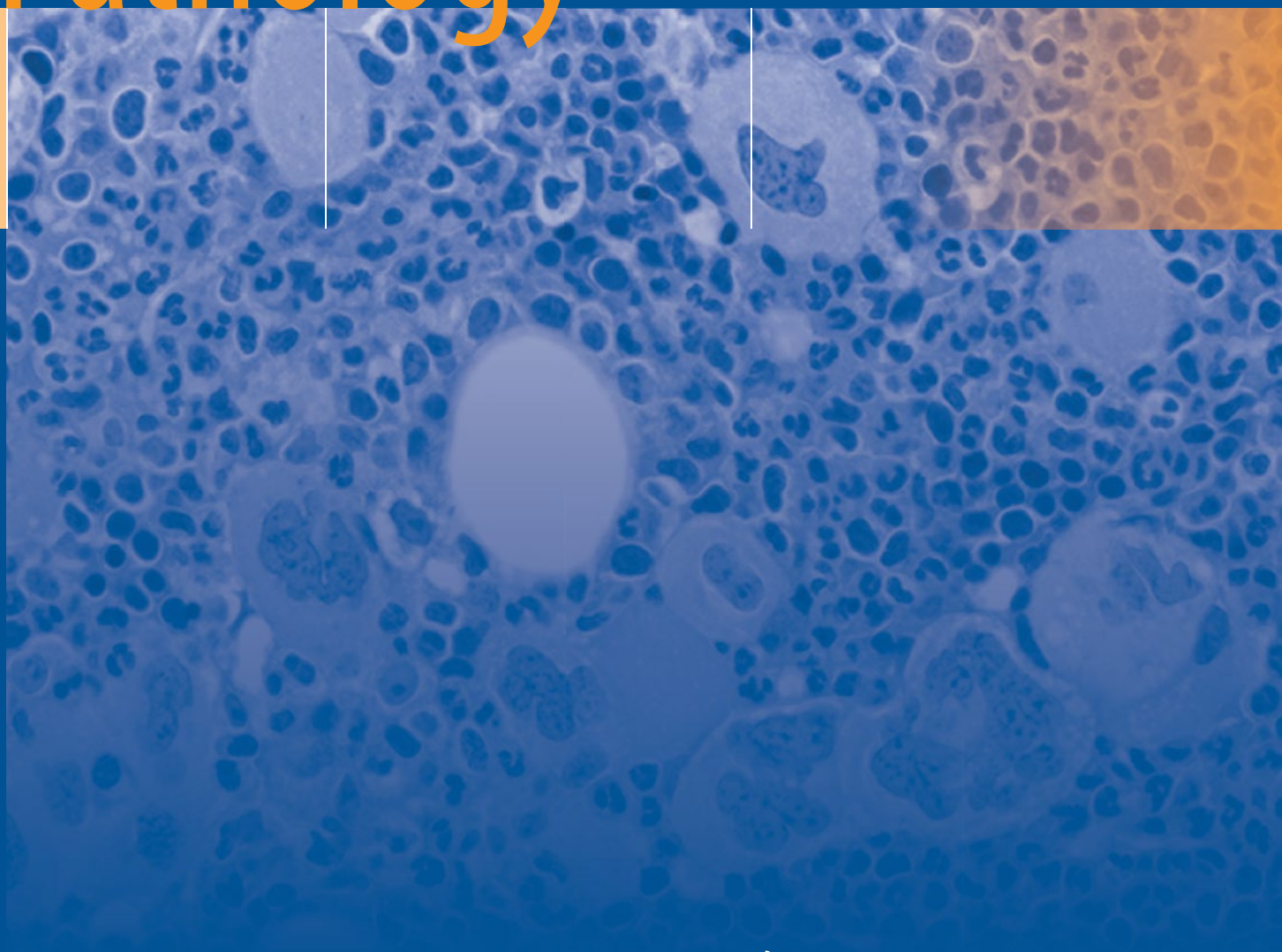
Tracy I. George
Daniel A. Arber
Editors

Atlas of Bone Marrow Pathology



Springer

Atlas of Anatomic Pathology

Series Editor

Liang Cheng
Indianapolis, Indiana
USA

This Atlas series is intended as a "first knowledge base" in the quest for diagnosis of usual and unusual diseases. Each atlas will offer the reader a quick reference guide for diagnosis and classification of a wide spectrum of benign, congenital, inflammatory, nonneoplastic, and neoplastic lesions in various organ systems. Normal and variations of "normal" histology will also be illustrated. Each atlas will focus on visual diagnostic criteria and differential diagnosis. It will be organized to provide quick access to images of lesions in specific organs or sites. Each atlas will adapt the well-known and widely accepted terminology, nomenclature, classification schemes, and staging algorithms. Each volume in this series will be authored by nationally and internationally recognized pathologists. Each volume will follow the same organizational structure. The first Section will include normal histology and normal variations. The second Section will cover congenital defects and malformations. The third Section will cover benign and inflammatory lesions. The fourth Section will cover benign tumors and benign mimickers of cancer. The last Section will cover malignant neoplasms. Special emphasis will be placed on normal histology, gross anatomy, and gross lesion appearances since these are generally lacking or inadequately illustrated in current textbooks. The detailed figure legends will concisely summarize the critical information and visual diagnostic criteria that the pathologist must recognize, understand, and accurately interpret to arrive at a correct diagnosis.This book series is intended chiefly for use by pathologists in training and practicing surgical pathologists in their daily practice. The atlas series will also be a useful resource for medical students, cytotechnologists, pathologist assistants, and other medical professionals with special interest in anatomic pathology. Trainees, students, and readers at all levels of expertise will learn, understand, and gain insights into the complexities of disease processes through this comprehensive resource. Macroscopic and histological images are aesthetically pleasing in many ways. This new series will serve as a virtual pathology museum for the edification of our readers.

More information about this series at http://www.springer.com/series/10144

Tracy I. George • Daniel A. Arber
Editors

Atlas of Bone Marrow Pathology

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Editors
Tracy I. George
Department of Pathology
University of New Mexico School of Medicine
Albuquerque, NM, USA

Daniel A. Arber
Department of Pathology
The University of Chicago
Chicago, IL, USA

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Thank you, Chris, for your unwavering support and understanding.

Tracy I. George

To Carol, James, and William.

Daniel A. Arber

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

We developed this atlas in order to provide a practical tool for the practicing pathologist and trainees in the field. Using experts in the field of diagnostic hematopathology, we have crafted individual chapters comprised of numerous high-quality images, useful tables, and diagrams that illustrate areas of diagnostic concern for pathologists, contrasting problem areas and morphologic mimics, as well as discussing the latest classification of neoplasms.

Our intent is not to create exhaustive, lengthy treatises on each disease entity. Instead, this atlas contains helpful hints from seasoned diagnosticians about how they approach an individual patient's biopsy and thus encompasses multiple modalities, from cytomorphology and histopathology to flow cytometry and genetic testing.

Key references are provided to help guide the reader and provide a starting point for further education. Our final result is an atlas of bone marrow pathology that can be used daily, from troubleshooting of difficult cases to recognition of unusual entities.

Please enjoy!

Albuquerque, NM, USA — Tracy I. George
Chicago, IL, USA — Daniel A. Arber

Contents

Contributors

Daniel A. Arber Department of Pathology, The University of Chicago, Chicago, IL, USA

Katherine R. Calvo, MD, PhD Department of Laboratory Medicine, National Institutes of Health Clinical Center, Bethesda, MD, USA

Joanna M. Chaffin, MD Department of Pathology, Medical College of Georgia at Augusta University, Augusta, GA, USA

Yi-Hua Chen, MD Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Devon Chabot-Richards, MD Department of Pathology, University of New Mexico Sciences Center, Albuquerque, NM, USA

Juehua Gao, MD, PhD Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Tracy I. George Department of Pathology, University of New Mexico School of Medicine, Albuquerque, NM, USA

Sandeep Gurbuxani, MBBS, PhD Department of Pathology, Section of Hematopathology, University of Chicago, Chicago, IL, USA

Matthew T. Howard, MD Division of Hematopathology, Mayo Clinic, Rochester, MN, USA

Rebecca L. King, MD Division of Hematopathology, Mayo Clinic, Rochester, MN, USA

Perikala Vijayananda Kumar, MD Department of Pathology, Shiraz Medical School, Shiraz, Fars, Iran

Jason H. Kurzer, MD, PhD Stanford University School of Medicine, Stanford, CA, USA

Lee J. McGhan, MD Department of Pathology, University of Arizona/Banner University Medical Center, Tucson, AZ, USA

Ahmad Monabati, MD Department of Pathology, Shiraz Medical School, Shiraz, Fars, Iran

Megan Parilla, MD Department of Pathology, University of Chicago Medical Center, Chicago, IL, USA

Maria A. Proytcheva, MD Department of Pathology, University of Arizona/Banner University Medical Center, Tucson, AZ, USA

Kaaren K. Reichard, MD Department of Laboratory Medicine and Pathology, Division of Hematopathology, Mayo Clinic, Rochester, MN, USA

Heesun J. Rogers, MD, PhD Department of Laboratory Medicine, Cleveland Clinic, Cleveland, OH, USA

Aaron Paul Rupp, MD Department of Pathology, University of New Mexico Center, Albuquerque, NM, USA

Natasha Marie Savage, MD Department of Pathology, Medical College of Georgia at Augusta University, Augusta, GA, USA

Kristian T. Schafernak, MD, MPH Department of Pathology and Laboratory Medicine, Phoenix Children's Hospital, Phoenix, AZ, USA

Min Shi, MD, PhD Department of Laboratory Medicine and Pathology, Division of Hematopathology, Mayo Clinic, Rochester, MN, USA

Luke R. Shier, MD Department of Pathology and Laboratory Medicine, University of Ottawa, Ottawa, ON, Canada

Payal Sojitra Department of Pathology, University of New Mexico School of Medicine, Albuquerque, NM, USA

Mohammad Vasef, MD Department of Pathology, University of New Mexico Health Sciences Center, Albuquerque, NM, USA

Girish Venkataraman, MD Department of Pathology, University of Chicago Medical Center, Chicago, IL, USA

Olga K. Weinberg, MD Pathology Department, Boston Children's Hospital, Boston, MA, USA

Carla S. Wilson, MD, PhD Department of Pathology, University of New Mexico Health Sciences Center and Tricore Reference Laboratories, Albuquerque, NM, USA

Qian-Yun Zhang, MD, PhD Department of Pathology, University of New Mexico, Albuquerque, NM, USA

Normal Bone Marrow

1

Heesun J. Rogers

The bone marrow examination is an important diagnostic procedure used for a wide variety of clinical conditions such as the diagnosis of myeloid or lymphoid neoplasms, various reactive conditions or metastatic, non-hematopoietic malignancies. Bone marrow examination is also used for confirmation or monitoring of a remission state, residual or recurrent disease state, or regeneration of bone marrow after various therapies. Bone marrow aspiration and biopsy of adequate quality are considered to represent overall bone marrow function.

A basic understanding of bone marrow structures and the correct identification of cells comprising normal bone marrow are very important in the interpretation of bone marrow pathology. The bone marrow is a well-organized structure confined in cortical bone and traversed by medullary or trabecular bone. The bone marrow has three components: hematopoietic cells, stroma/microenvironment, and medullary bone. Hematopoietic cells are embedded in a connective tissue stroma in intertrabecular spaces of medullary bone. The bone marrow is almost entirely occupied by hematopoietic cells, with the highest cellularity at birth or early infancy. The hematopoietic cells gradually decrease in the bone marrow with aging, and the bone marrow is replaced by adipose cells (fat cells). Hematopoietic cells derived from multipotent stem cells can be further differentiated into several lineage cells: erythrocytes, granulocytes, monocytes, megakaryocytes, and lymphocytes.

Tables 1.1, 1.2, and 1.3 list the characteristic cytologic features of erythroid cells, granulocytic cells, and megakaryocytic cells. These tables illustrate the various stages of maturation from the earliest recognizable immature cells to mature cells in the bone marrow. Erythroid precursor cells (normoblast or erythroblast) develop adjacent to macrophages and are subdivided into pronormoblasts, basophilic normoblasts, polychromatophilic normoblasts, and orthochromic normoblasts. Immature granulocytic cells develop adjacent to trabecular surfaces or arterioles and are further subdivided into blasts, promyelocytes, myelocytes, metamyelocytes, band neutrophils, and segmented neutrophils. Megakaryocytes, the largest hematopoietic cells in bone marrow, can be easily identified adjacent to sinusoids, but megakaryoblasts or immature megakaryocytes are often difficult to recognize in the bone marrow and can be readily identified in conjunction with immunohistochemistry or immunophenotype.

The marrow stroma is composed of fibroblasts, macrophages, adipose cells, osteoblasts, osteoclasts, sinusoids or capillaries, and endothelial cells.

In this chapter, characteristic cytologic and histologic features of various types of hematopoietic cells (particularly a spectrum of maturing hematopoietic cells) and stromal cells observed in normal bone marrow are described with representative pictures (Figs. 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 1.10, 1.11, 1.12, 1.13, 1.14, 1.15, 1.16, 1.17, 1.18, 1.19, 1.20, 1.21, 1.22, 1.23, 1.24, 1.25, 1.26, 1.27, and 1.28). Bone marrow cells that are morphologically similar and easy to misidentify are illustrated with a comparison of their cytologic features.

H.J. Rogers (✉)
Department of Laboratory Medicine, Cleveland Clinic,
Cleveland, OH, USA
e-mail: rogersj5@ccf.org

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Table 1.1 Maturation of erythroid cells in bone marrow

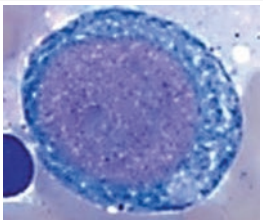
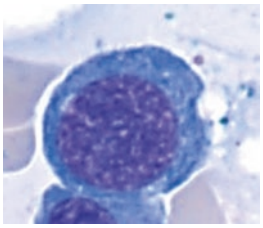
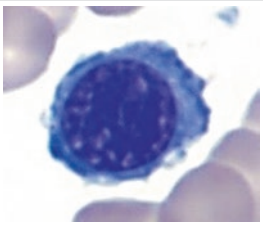
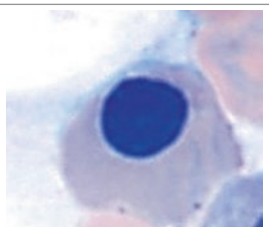
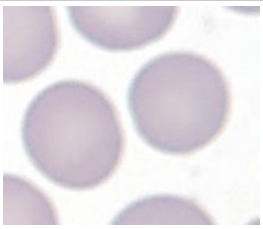
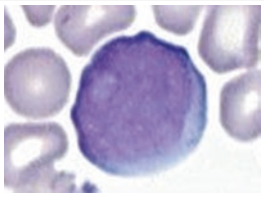
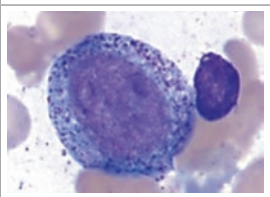
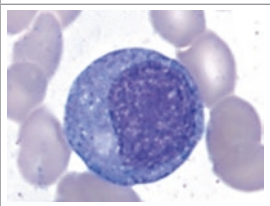
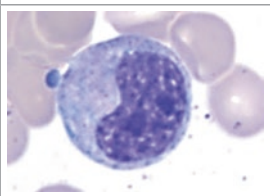
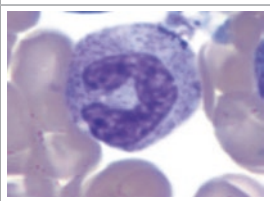
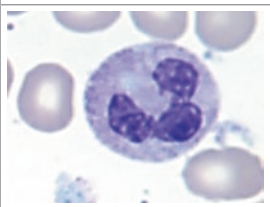
Cell type	Characteristic morphology	Description
Pronormoblast (proerythroblast)		The most immature and largest cells in erythroid lineage (12–24 μm), relatively high nuclear to cytoplasmic (N/C) ratio (7–8:1), round to slightly oval nucleus, finely reticulated chromatin, prominent nucleoli (≥ 1), and agranular basophilic cytoplasm
Basophilic normoblast		Smaller cells (10–17 μm) than pronormoblast, round nucleus, high N/C ratio (6:1), open to slightly condensed chromatin, distinct parachromatin, rarely visible or absent nucleoli in later stage, and deep basophilic cytoplasm
Polychromatophilic normoblast		Smaller cells (10–15 μm) and lower N/C ratio (4:1) than basophilic normoblasts, round nucleus with condensed chromatin, often cartwheel appearance, visible perinuclear halo, no nucleoli, and blue-gray to pink-gray cytoplasm
Orthochromic normoblast		More mature and smaller cells (8–12 μm) than polychromatophilic normoblast, abundant cytoplasm (N/C ratio 1:2) with pink-orange and minimally basophilic color similar to erythrocytes, round nucleus, and densely condensed or pyknotic chromatin
Erythrocyte		The most mature cells (7–8.5 μm), pink-orange to salmon color, and no nucleus

Table 1.2 Maturation of granulocytic cells in the bone marrow

Cell type	Characteristic morphology	Description
Myeloblast		The most immature granulocytic cells (15–20 μm), with high N/C ratio (4–7:1), round to oval nucleus, fine to reticular chromatin with distinct nucleoli (1–5), and moderately basophilic cytoplasm with absent or minimal azurophilic granules
Promyelocyte		Slightly larger cells (14–24 μm) than myeloblasts, with high N/C ratio (3–5:1), eccentric round to oval nucleus, slightly coarse or finely reticular chromatin, distinct nucleoli (1–3), basophilic cytoplasm with paranuclear hof and prominent azurophilic (primary) granules, which may overlie the nucleus
Myelocyte		Slightly smaller cells (10–18 μm) than blasts, with more abundant cytoplasm (N/C ratio 1–2:1), eccentric round to oval nucleus, more condensed chromatin, no nucleoli, bluish to pink cytoplasm with paranuclear hof, abundant lilac (secondary) granules, and scattered few azurophilic (primary) granules
Metamyelocyte		Size similar to or slightly smaller (10–18 μm) than myelocytes, with abundant cytoplasm (N/C ratio 1–1.5:1), indented or kidney-shaped nucleus (indentation less than half the width of the nuclear margin), condensed chromatin, no nucleoli, pinkish cytoplasm with many secondary granules and rare primary granules
Band neutrophil		More mature cells (10–18 μm) similar to metamyelocytes, abundant cytoplasm (N/C ratio 1:1.2–1.5), indented or band-like or sausage-like nucleus (indentation more than half the width of the nuclear margin), condensed chromatin, no nucleoli, and pinkish cytoplasm with abundant secondary granules
Segmented neutrophil		The most mature cells (10–18 μm), with abundant cytoplasm, more condensed nucleus with 3 to 5 distinct lobes connected by thin filaments, and pinkish cytoplasm packed with secondary granules