

Non-Neoplastic Disorders of Bone Marrow

*AFIP Atlases of
Tumor and
Non-Tumor Pathology*



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AFIP ATLASES OF TUMOR AND NON-TUMOR PATHOLOGY

Fifth Series

Fascicle 26

NON-NEOPLASTIC DISORDERS OF BONE MARROW

by

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DEDICATIONS

To Mom and Dad, who met working at the Passavant Hospital Hematology Laboratory, thank you for a lifetime of love and support.

Elizabeth L. Courville, MD

To Dr. Robert McKenna, for his extraordinary mentorship, and to Marc Schulte, for his unwavering support on the home front.

Michael A. Linden, MD, PhD

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Robert P. Hasserjian, MD



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We would also like to recognize the many individuals who contributed photomicrographs and illustrative material of these often rare entities; these contributions are cited throughout the figure legends. The technical expertise of our laboratory partners, whose diligence ensures high-quality specimens and images, has similarly strengthened this fascicle.

Finally, we are deeply appreciative of the longstanding tradition of excellence established by the American Registry of Pathology and the Armed Forces Institute of Pathology (ARP/AFIP) and the authors of prior Fascicles, whose scholarship continues to guide and inspire the production of these volumes.

Elizabeth L. Courville, MD
Michael A. Linden, MD, PhD
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EDITOR'S NOTE

The Atlases of Tumor Pathology have a long and distinguished history. They were first conceived at a cancer research meeting held in St. Louis in September 1947, as an attempt to standardize the nomenclature of neoplastic diseases. The first series was sponsored by the National Academy of Sciences-National Research Council. The organization of this formidable effort was entrusted to the Subcommittee on Oncology of the Committee on Pathology, and Dr. Arthur Purdy Stout was the first editor-in-chief. Many of the illustrations were provided by the Medical Illustration Service of the Armed Forces Institute of Pathology (AFIP), the type was set by the Government Printing Office, and the final printing was done at the Armed Forces Institute of Pathology. The American Registry of Pathology (ARP) purchased the Fascicles from the Government Printing Office and sold them virtually at cost. Over a period of 20 years, approximately 15,000 copies each of nearly 40 Fascicles were produced. The worldwide impact of these publications over the years has largely surpassed the original goal. They quickly became among the most influential publications on tumor pathology, primarily because of their overall high quality, but also because their low cost made them easily accessible the world over to pathologists and other students of oncology.

Upon completion of the first series, the National Academy of Sciences-National Research Council handed further pursuit of the project over to the newly created Universities Associated for Research and Education in Pathology (UAREP). The Second Series was started, generously supported by grants from the AFIP, the National Cancer Institute, and the American Cancer Society. Dr. Harlan I. Firminger became the editor-in-chief and was succeeded by Dr. William H. Hartmann. The Second Series Fascicles were produced as bound volumes instead of loose leaflets. They featured a more comprehensive coverage of the subjects, to the extent that the Fascicles could no longer be regarded as "atlases" but rather as monographs describing and illustrating in detail the tumors and tumor-like conditions of the various organs and systems.

Dr. Juan Rosai was appointed as editor-in-chief of the Third Series, and Dr. Leslie Sobin became associate editor. A distinguished Editorial Advisory Board was also convened, and these outstanding pathologists and educators played a major role in the success of this series, the first publication of which appeared in 1991 and the last (number 32) in 2003.

The same organizational framework applied to the Fourth Series, meticulously edited by Dr. Steven Silverberg with Dr. Ronald DeLellis as the associate editor. With UAREP and AFIP no longer functioning, ARP remained the responsible organization. The Fourth Series volumes were hardbound with illustrations almost exclusively in color. There was also an increased emphasis on the cytopathologic (intraoperative, exfoliative, or fine needle aspiration) and molecular features that are important

in diagnosis and prognosis. At the time of the Fourth Series, ARP also produced Atlases of Non-Tumor Pathology; these volumes were numbered separately from the tumor volumes.

As in the prior series, the goal of the Fifth Series includes a continuous attempt to correlate, whenever possible, the nomenclature used in the Fascicles with that proposed by the World Health Organization Classification of Tumors, as well as to ensure a consistency of style. Including molecular diagnostics is more important than ever, as is the availability of an online component, a more nimble website (www.arppress.org), and a social media presence. Now in this series, the tumor and non-tumor volumes are combined and consecutively numbered as the Atlases of Tumor and Non-Tumor Pathology. Close cooperation between the various authors and their respective liaisons from the Editorial Board will continue to be emphasized in order to minimize unnecessary repetition and discrepancies in the text and illustrations.

Particular thanks are due to the members of the Editorial Advisory Board, our reviewers, the editorial and production staff, and the individual Fascicle authors for their ongoing efforts to ensure that this series is a worthy successor to the previous four.

Jason L. Hornick, MD, PhD



PREFACE

This Fascicle, *Non-Neoplastic Disorders of Bone Marrow*, is devoted to the evaluation and interpretation of bone marrow and peripheral blood specimens from both adult and pediatric patients. The primary focus of this volume is the spectrum of acquired non-neoplastic processes that affect the blood and marrow. We also include selected clonal non-neoplastic conditions as well as germline or congenital conditions that affect the blood and bone marrow. Neoplasms are discussed when they form an essential part of the differential diagnosis. Key concepts and comparisons are highlighted through frequent summary tables designed to emphasize important morphologic, immunophenotypic, genetic, and clinical features of these disorders, which can often mimic malignant conditions.

The Fascicle is organized into ten chapters. The first three chapters provide foundational material: an overview of normal bone marrow and peripheral blood, guidance on marrow collection and processing, and a discussion of sample adequacy and artifact. In chapter 2, we provide a practical approach to bone marrow and blood evaluation. The remaining chapters are organized by etiology rather than specific blood or bone marrow cell type, since many conditions that affect the hematopoietic system manifest in a myriad of cell types in the blood and/or marrow. Chapters 4 through 8 address these distinct etiologies: paraneoplastic phenomena, autoimmune diseases, metabolic disorders, nutritional deficiencies, and the effects of toxins and medications. The last two chapters are devoted to clonal and congenital disorders that have blood and marrow manifestations.

To facilitate linking specific pathologic findings in blood or bone marrow to the discussions of their differential diagnoses, we have included two comprehensive cross-referencing tables in this preface. Table 1 lists bone marrow features (such as fibrosis, changes in cellularity, dysplasia) and the relevant chapters where they are discussed, while Table 2 similarly lists specific peripheral blood findings (e.g., neutropenia, inclusions, circulating blasts). For ease of use, the relevant chapter for each differential diagnosis is provided, enabling readers to move efficiently between patterns of abnormality and the potential diagnoses that may explain these findings.

Our goal in assembling this Fascicle is to offer a practical, morphologically-grounded resource for practicing pathologists and hematopathologists, trainees, and all clinicians who rely on blood and marrow examination in patient care. Non-neoplastic disorders of the bone marrow frequently require the integration of subtle morphologic clues with the clinical context and laboratory data; pathologists also must know what confirmatory ancillary tests to order (and which scenarios require testing). The illustrations and tables in this volume support an integrative approach and serve as a useful reference in both routine practice and complex diagnostic evaluations.

Importantly, these non-neoplastic disorders can mimic malignant hematologic conditions, potentially leading to misdiagnosis and the administration of inappropriate therapy. Hematopathology training curricula and educational resources tend to focus more on hematologic malignancies, and thus, trainees and practicing pathologists are often less comfortable when confronted with the differential diagnosis of a benign hematologic process. We hope this Fascicle fills this gap by illustrating the distinct morphologic characteristics and practical approach to the broad spectrum of benign blood and bone marrow disorders.

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Finding	Associated Conditions	Chapter Discussed
General Bone Marrow Findings		
Hypercellularity	Very non-specific: can be seen in a variety of non-neoplastic conditions including marrow regeneration, drug effect, nutritional deficiency, infection, autoimmune processes, paraneoplastic conditions, and congenital conditions	Multiple
Hypocellularity	Infections	4
	Aplastic anemia	5, 6
	Systemic lupus erythematosus	6
	Copper deficiency	7
	Alcohol toxicity, chronic benzene exposure	8
	Graft versus host disease (GVHD)	8
	Cytotoxic therapies (methotrexate and other cytotoxic agents)	8
	TNF α -inhibitors	8
	Paroxysmal nocturnal hemoglobinuria (PNH)	9
	Germline conditions, including Fanconi anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, germline mutations in RUNX1, congenital amegakaryocytic thrombocytopenia	10
Fibrosis	Felty syndrome	6
	Systemic lupus erythematosus	6
	Autoimmune myelofibrosis	6
	TAFRO syndrome	6
	Renal osteodystrophy (paratrabecular fibrosis)	7
	Post-stem cell transplant for advanced fibrotic myeloproliferative neoplasm	8
	Chronic benzene exposure	8
	Thrombopoietin receptor agonists (TPO mimetics)	8
Amorphous material	Bone crush artifact	3
	Serous atrophy, edema (interstitial amorphous material)	7
	Chemoablation	8
Necrosis	Infection (mycobacterium tuberculosis, coxiella)	4
	Hemophagocytic lymphohistiocytosis	4
	Granulocyte-colony stimulating factor (G-CSF)	8
	Sickle cell disease	10
Myeloid Precursors		
Vacuoles	Copper deficiency	7
	VEXAS syndrome	9
Granulocytic left-shift	Infection	4
	Felty's syndrome	6
	Copper deficiency	7
	Granulocyte-colony stimulating factor (G-CSF)	8
	Marrow recovery	8
Granulocytic maturation arrest	Infection	4
	Levamisole exposure	8
	Medications (trimethoprim and sulfamethoxazole [Bactrim], ticlopidine, busulfan, methamizole, ethosuximide, and chlorpromazine)	8
	Cyclic neutropenia, Chediak-Higashi syndrome, severe congenital neutropenia	10
Granulocytic hyperplasia	Infection	4
	Felty's syndrome	6
	Paraneoplastic leukemoid reaction	7
	Granulocyte-colony stimulating factor (G-CSF)	8

Table 1, continued

Finding	Associated Conditions	Chapter Discussed
Hypergranularity (retained primary granules)	Infection	4
	Granulocyte-colony stimulating factor (G-CSF)	8
Giant band forms	Megaloblastic anemia (nutritional)	7
	Medication (methotrexate, 5-fluorouracil, hydroxyurea)	8
Dysplasia (hypogranular/abnormal segmentation)	Medication (tacrolimus, mycophenylate mofetil)	8
	Post-chemotherapy	8
	Dyskeratosis congenita, Shwachman-Diamond syndrome, severe congenital neutropenia	10
Eosinophilia	Paraneoplastic eosinophilia/hypereosinophilia	7
	Lymphocytic variant of hypereosinophilic syndrome	9
	Infection	4
Increased Blasts (typically mild increase)	Infection	4
	Medication (G-CSF, romiplostim)	8
	Marrow recovery	8
Megakaryocytes		
Abnormal morphology	HIV (scant cytoplasm, hyperchromatic nuclei)	4
	Germline conditions (Table 10-7)	10
	Drug/medication (Table 8-1)	8
	POEMS	5
Increased/Decreased in number	HIV (increased megakaryocytes)	4
	POEMS (increased megakaryocytes)	5
	Congenital amegakaryocytic thrombocytopenia, thrombocytopenia with absent radii syndrome (decreased megakaryocytes)	10
	Immune thrombocytopenic purpura (increased megakaryocytes)	6
	Aplastic anemia (decreased megakaryocytes)	6
Clustering	Marrow regeneration following chemotherapy	8
	Immune thrombocytopenic purpura	6
	POEMS	5
Plasma Cells		
Polytypic plasmacytosis	Non-specific	1
	Infection (various, including HIV)	4
Minor clonal population	Monoclonal gammopathy of undetermined significance (MGUS)	9
Immunoglobulin inclusions/pseudo-inclusions (Russell bodies, Mott cells, Dutcher bodies)	Non-specific	1
Lymphocytes		
Lymphoid aggregates	Normal component	1
	Infection	4
	Autoimmune/immune mediated	5,6
Minor clonal lymphocyte population	Monoclonal B cell lymphocytosis	9
	T-cell clone of uncertain significance	9
Hematogones	Normal component	1
	Hyperplasia following stem cell transplant or chemotherapy	8
Erythroid Precursors		
Hyperplasia	Autoimmune hemolytic anemia	5
	Copper deficiency	7
	Alcohol toxicity	8

Table 1, continued		
Finding	Associated Conditions	Chapter Discussed
Hyperplasia (cont.)	Medication (including hypomethylating agents, arsenic trioxide, erythropoietin)	8
	Paroxysmal nocturnal hemoglobinuria	9
	Sickle cell disease	10
	Congenital disease (thalassemia, congenital dyserythropoietic anemia, Fanconi anemia)	10
Ring sideroblasts	HIV	4
	Copper deficiency	7
	Alcohol toxicity	8
	Medication (including isoniazid, chloramphenicol, linezolid, penicillamine, and triethylene tetramine dihydrochloride)	8
	Congenital disease (thalassemia, congenital sideroblastic anemia)	10
Dysplasia	Non-specific finding seen as marrow response to anemia, in nutritional deficiency, and in germline conditions, among others	?
Erythroid cytoplasmic vacuoles	Copper deficiency	7
	Chronic alcohol exposure	8
	VEXAS	9
Pure red cell aplasia	Infection (including parvovirus B19)	4
	Variety of secondary causes including lymphoproliferative disorders, thymoma	6
Maturation arrest	Parvovirus B19	4
Megaloblastic change	Copper deficiency; Vitamin B12/folate deficiency	7
	Alcohol toxicity	8
	Medications	8
Abnormal Histiocytes		
Histiocytes with inclusions	Infections	4
	Congenital metabolic conditions	10
Histiocytes with vacuoles	Congenital metabolic conditions	10
	Non-specific finding	
Hemophagocytosis	Infections, especially EBV	4
	Paraneoplastic, especially EBV+ lymphomas	7
	Congenital/familial causes	10
	Drug-induced	8
Histiocytes with crystals	Paraneoplastic (crystal-storing histiocytosis)	7
	Cystinosis	10
Granulomas	Infections	4
	Sarcoidosis	
	Non-specific finding	

Table 2
ABNORMAL PERIPHERAL BLOOD FINDINGS AND
POTENTIAL NON-NEOPLASTIC ASSOCIATIONS/CAUSES

Finding	Associated Conditions	Chapter Discussed
White Blood Cells		
Neutrophilia	Asplenia	1
	Infection	4
	Paraneoplastic leukemoid reaction	5
	CVID (mild neutrophilia)	6
	Medication (G-CSF, GM-CSF, glucocorticoids, lithium)	8
Neutropenia	Paraneoplastic (immune mediated)	5
	Autoimmune	6
	Copper deficiency	7
	Medication effect (various)	8
	Levamisole exposure	8
	Leukocyte protein abnormalities (Duffy-null associated neutrophil count, cyclic neutropenia, Chediak-Higashi Syndrome)	10
	Germline conditions (including severe congenital neutropenia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome)	10
Vacuoles	Monocytes (occasional vacuoles): normal	1
	Neutrophils: Infection	4
	Any leukocyte: Jordan's anomaly	10
	Lymphocytes: sialidosis	10
	Excess EDTA exposure	
Inclusions	Monocytes (morulae, erlichiosis)	4
	Granulocytes (morulae, erlichiosis and anaplasmosis)	4
	Granulocytes/monocytes: MYH9-related disorders	10
Microorganisms in neutrophils or monocytes	Infections	4
Döhle bodies	Infection	4
	Paraneoplastic	5
	Hematopoietic growth factors/G-CSF	8
Myeloid left-shift	Marrow involvement by metastatic disease	3
	Infection	4
	Marrow recovery after therapy	8
	Hematopoietic growth factors/G-CSF	8
Hypogranulation	Poor staining quality	3
Abnormal granulation	Alder-Reilly anomaly	10
	Chediak-Higashi	10
Toxic granulation	Infection	4
	Paraneoplastic reaction	5
	Hematopoietic growth factors/G-CSF	8
Hypersegmentation	Megaloblastic anemia (nutritional)	7
	Medication (methotrexate, 5-fluorouracil, hydroxyurea)	8
Hyposegmentation	Medication (tacrolimus, mycophenylate mofetil)	8
	Pelger-Huët anomaly/syndrome	10
Eosinophilia	Infection	4
	Paraneoplastic hypereosinophilia	5
	Castleman/TAFRO syndrome	6
	Medication (penicillins, sulfa drugs, allopurinol, diphenylhydantoin)	8
	Medication (DRESS syndrome)	8
	Lymphocytic variant of hypereosinophilic syndrome	9

Table 2, continued

Finding	Associated Conditions	Chapter Discussed
Circulating blasts (in low numbers)	Medication (G-CSF, romiplostim)	8
	Marrow recovery	8
	As component of myeloid left-shift (see separate listing)	
	Down Syndrome/Transient Abnormal Myelopoiesis (may moderate or high blast percentage)	10
Lymphocytosis	Transient stress lymphocytosis in patients with emergency medical conditions	1
	Infection, commonly viral and occasionally bacterial	4
	Castleman/TAFRO	6
	Polyclonal B lymphocytosis	6
	Post-stem cell transplant (large granular lymphocytes)	8
	Dasatinib therapy (large granular lymphocytes)	8
	Monoclonal B cell lymphocytosis	9
Atypical/abnormal appearing lymphocytes	Infection, may be striking with infectious mononucleosis	4
	CAR-T therapy	8
Basophilia	Filarial infections, rarely viral and mycobacterial infections	4
Monocytosis	Asplenia	1
	Infection	4
	CVID	6
	Marrow recovery after therapy	8
	Hematopoietic growth factors/G-CSF	8
Plasma cells	Viral infections	4
Platelets		
Thrombocytosis	Asplenia	1
	Infection	4
	Paraneoplastic	5
	Chronic inflammatory state (acute phase reactant)	1
	Iron deficiency	7
Thrombocytopenia	Pseudothrombocytopenia	1
	Marrow involvement by metastatic disease	3
	Infection	4
	Autoimmune/Immune Mediated	5, 6
	Nutritional Deficiency	7
	Toxins/Drugs	8
	Germline conditions (including mutations in RUNX1, ANKRD26, ETV6; SAMD9/SAMD9L disorders; congenital megakaryocytic thrombocytopenia; thrombocytopenia with absent radii syndrome)	10
	Storage Disorders	10
Small platelets	Wiskott-Aldrich syndrome	10
Large platelets	MYH9-related disorders	10
	Platelet-type vWBD	10
	Hermansky-Pudlak syndrome	10
Platelet granulation abnormalities	Hermansky-Pudlak syndrome (pale)	10
	Grey-platelet syndrome (pale)	10
	Chediak-Higashi syndrome (hypergranulated)	10
Extrinsic Elements in Blood		
Megakaryocytes	Rarely seen in normal	1
Endothelial cells	Rarely seen in normal	1
Parasites	Infections	4

Table 2, continued

Finding	Associated Conditions	Chapter Discussed
Red Blood Cells		
Microorganisms	Infections	4
Erythrocytosis/ polycythemia	TEMPI syndrome	4
	POEMS syndrome	4
	Drugs/Medications	8
	Hypoxia	
Nucleated red blood cells (nRBC)	Asplenia	1
	Leukoerythroblastic blood picture due to carcinoma (chap. 1) some drugs (chap. 8), or (rarely) autoimmune myelofibrosis (chap. 6)	1, 8, 6
	Normal in neonates	1
Increased poikilocytosis	Nonspecific finding, can be seen in asplenia, iron deficiency, hemo- globinopathy, and hemolysis, among other causes; RBC poikilo- cyte shape(s) can provide clues to the physiologic/disease state	1
Basophilic stippling	Lead poisoning (coarse stippling)	8
	Thalassemia/hemoglobinopathy (fine stippling)	10
	Congenital dyserythropoietic anemia	10

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