CHAPTER

07

Myeloid disorders

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Introduction

The term "myeloid" derives from the Greek *myelos*, meaning "marrow." Sometimes the term "myeloid" is used to describe hematological conditions or diseases not involving the lymphoid tissues or lymphocytes. "Myeloid" is also used to describe disorders primarily involving granulocytes (neutrophils, eosinophils, or basophils) and monocytes. Tissue macrophages (histiocytes), Langerhans cells, and interdigitating dendritic cells also arise from monocytic progenitors or precursors. Other important immunoregulatory dendritic cell types and mast cells derive from marrow progenitors that are distinct from myeloid and monocytic progenitors. This chapter covers disorders of granulocytes, monocytes, histiocytes, dendritic cells, and mast cells. The myeloproliferative disorders (ie, the clonal disorders of myeloid origin), including polycythemia vera, essential thrombocytosis, idiopathic myelofibrosis/myeloid metaplasia, and chronic myelogenous leukemia, are described in Chapter 8.

Granulocytes: neutrophils, eosinophils, and basophils

The term "granulocytes" refers to circulating neutrophils, eosinophils, and basophils, although, because of their predominance in the blood, the terms "neutrophil" and "granulocyte" are sometimes used synonymously. The names for these cells originated with the work of a medical student, Paul Ehrlich. In 1877 he developed the system of aniline dyes that allowed the clear definition of the nucleus, cytoplasm, and other features of white blood cells, as examined on dried films on glass slides. Counting and carefully examining white blood cells on stained blood films remain cornerstones for diagnosing many infectious, inflammatory, and malignant diseases. Normal values for the differential count for leukocytes in the blood are shown in Table 7-1.

Neutrophils are a critical component of the innate immune response, and persistent neutropenia is associated with a marked susceptibility to infection. Conversely, there is increasing evidence that neutrophils may be a major contributor to tissue damage in inflammatory diseases. Thus, regulation of the level of blood neutrophils may be important in controlling both infectious and inflammatory diseases. Neutrophil homeostasis in the blood is regulated at 3 levels: neutrophil production in the bone marrow (granulopoiesis), neutrophil release from the bone marrow to blood, and neutrophil clearance from the blood. Under normal conditions, neutrophils are produced exclusively in the bone marrow, where it is estimated that 10^{12} are generated daily. Mature neutrophils are selectively released from the bone marrow to the blood in a regulated fashion. Once in the circulation, neutrophils are cleared rapidly with a half-life of only 6–8 hours.

Granulopoiesis

Granulocytic differentiation of hematopoietic stem cells is regulated by the coordinated expression of a number of key myeloid transcription factors, including PU.1, CCAAT enhancer binding protein α (C/EBPα), C/EBPε, and GFI-1 (see Chapter 2). A number of hematopoietic growth factors provide extrinsic signals that regulate granulopoiesis (see Chapter 3). The most important of these is granulocyte colony-stimulating factor (G-CSF), which stimulates the proliferation of granulocytic precursors, reduces the average transit time through the granulocytic compartment, and stimulates

Table 7-1 Normal leukocyte values in peripheral blood.

(a) Adults

	Cells/mm^{3*}	
Cell type	**Median**	**Range**
All leukocytes (white blood cells)	7000	4,300–10,000
Total neutrophils	4000	1800–7200
Band neutrophils	500	100–2000
Segmented neutrophils	3500	1000–6000
Lymphocytes	2500	1500–4000
Monocytes	450	200–900
Eosinophils	150	0–700
Basophils	30	0–150

*To calculate the number of cells per litre, multiply by 10^6.

(b) Children

Age	All leukocytes (cells/mm^3)	Neutrophils	Lymphocytes	Monocytes	Eosinophils
Neonate	9,000–38,000 (range)	5,000–28,000	2,000–11,500	1,100–1,200	400–500
1 week–1 month	5,000–21,000	1,000–10,000	2,000–17,000	700–1,100	300–500
6 months–2 years	6,000–17,500	1,000–8,500	3,000–13,500	500–600	300
4–8 years	4,500–15,500	1,500–8,500	1,500–8,000	400–500	200–300
10–16 years	4,500–13,500	1,800–8,000	1,200–6,500	400	200

Pediatric data: adapted from Geaghan SM. Normal blood values: selected reference values for neonatal, pediatric, and adult populations. In: Hoffman R, Benz EJ, Shattil SJ, et al., eds. Hematology: Basic Principles and Practice. 3rd ed. Philadelphia: Churchill Livingstone; 1999.

neutrophil release from the bone marrow. As discussed later in the chapter, disruption of normal granulopoiesis is a common cause of congenital and acquired neutropenia.

Neutrophil release from the bone marrow

Neutrophils, under normal conditions, are produced solely in the bone marrow and are released into the blood in a regulated fashion to maintain homeostatic levels of circulating neutrophils. The bone marrow provides a large reservoir of mature neutrophils that can be readily mobilized in response to infection. A broad range of substances has been shown to induce neutrophil release from the bone marrow, including chemokines, cytokines, microbial products, and various other inflammatory mediators (eg, C5a). Recent evidence suggests that the chemokine stromal-derived factor-1 (SDF-1, or CXCL12) plays a key role in regulating neutrophil trafficking in the bone marrow; this issue will be discussed in detail in the section on WHIM syndrome.

Neutrophil extravasation

Neutrophils in the circulation loosely attach and subsequently adhere to vascular endothelium in response to the local production of inflammatory cytokines and chemokines (Figure 7-1). Selectins mediate neutrophil rolling and β_2-integrins' firm adherence and vascular transmigration. Indeed, deficiency of selectin ligands or β_2-integrins causes leukocyte adhesion deficiency (LAD), a rare syndrome manifested by normal neutrophil production but impaired emigration to sites of inflammation.

Once emigrated to the inflammatory site, neutrophils function primarily as tissue phagocytes. These vital functions depend upon several critical features of these cells. Surface receptors for immunoglobulins and complement enhance ingestion and killing of microorganisms. Within the cell, the reduced nicotinamide-adenine-dinucleotide phosphate (NADPH) oxidase system, enzymes found in the cell's primary and secondary granules, and cytoplasmic glycogen are involved in the intracellular oxidative burst that accompanies phagocytosis and in the killing and digesting of microorganisms. Maintenance of both the supply of cells and the integrity of all of these functions is critical for normal host defense mechanisms. Diseases affecting each of these features and functions of neutrophils result in enhanced susceptibility to infection (see discussion later in the chapter).

Normally, the marrow contains only a very small proportion of eosinophils and basophils. The granules of eosinophils contain histamine and proteins important for the killing of parasites. Eosinophil production is increased, and eosinophilia

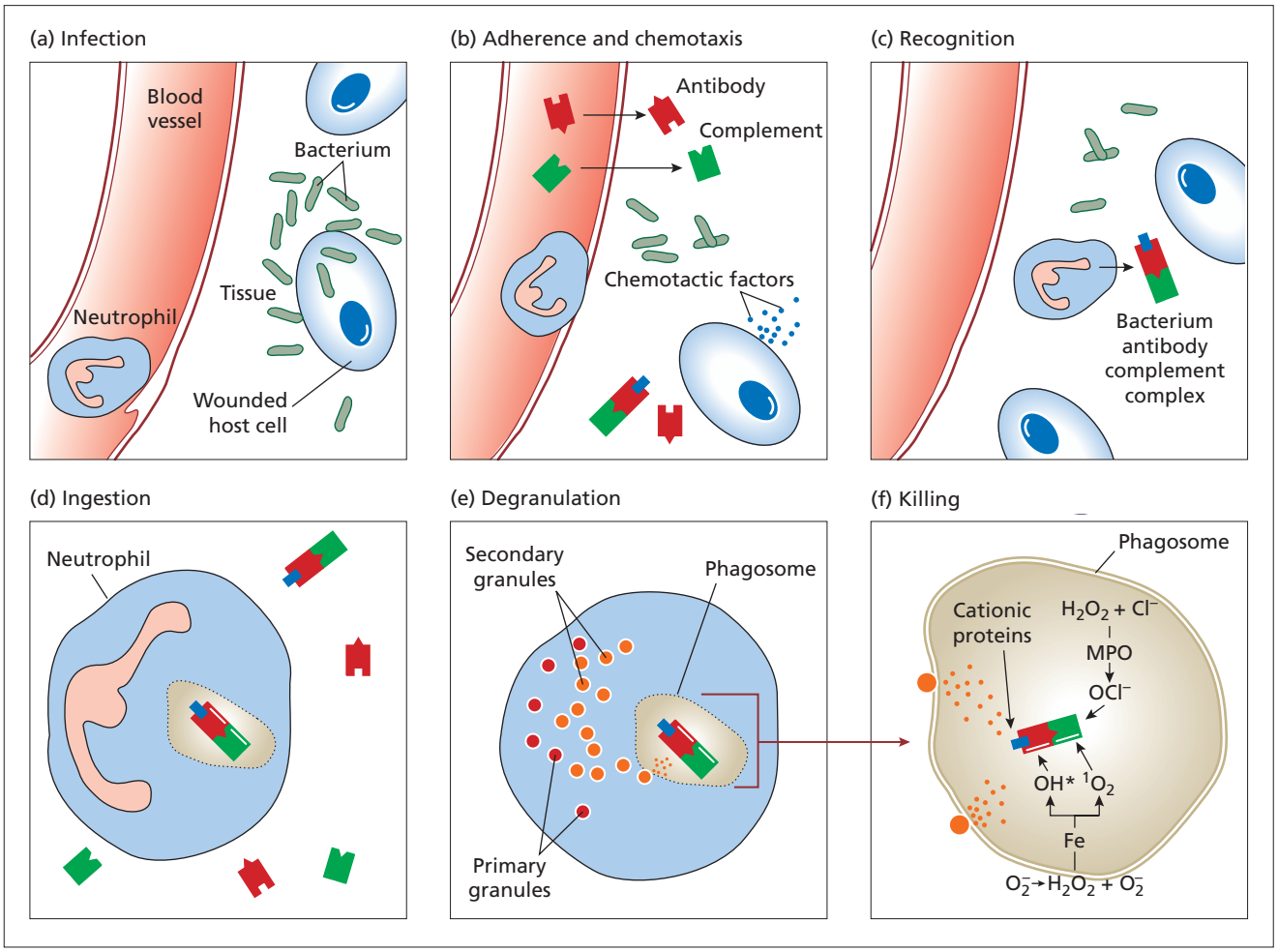


Figure 7-1 The neutrophil response to bacterial invasion involves several stages. A bacterium infects a host cell and injures it (a). Bacterial products, antibodies, and complement cause the release of chemotactic factors, which activate a neutrophil in the adjacent blood vessel. The neutrophil adheres to the vessel wall and undergoes chemotaxis and diapedesis into tissue (b) to follow the chemoattractants to their sites of generation or expression. The neutrophil recognizes (c) and ingests (d) the bacterium–antibody–complement complex, forming a phagosome. The neutrophil then undergoes degranulation, a process in which granule membranes fuse with the plasma membrane (e). Degranulation releases various enzymes and enhances oxidative metabolism, the products of which are bactericidal (f). For example, hydrogen peroxide (H_2O_2), produced from superoxide (O_2^-) can interact with O_2^- in the presence of iron (Fe) to produce hydroxyl radicals (OH^-) and singlet oxygen ($^1O_2$), both of which are highly toxic to bacteria. In addition, H_2O_2 and chloride (Cl^-) combine in the presence of the myeloperoxidase (MPO) released in the phagosome to produce hypochlorite (OCl^-), which is also bactericidal. (Copyright 2000, WebMD Corp. All rights reserved.)

(ie, $>0.7 \times 10^9$/L) occurs in many allergic disorders (ie, asthma, allergic rhinitis, or dermatitis), parasitic infections, collagen vascular diseases, and drug reactions. Eosinophilia also frequently occurs with myeloproliferative disorders and is the hallmark feature of the hypereosinophilic syndrome, a disorder characterized by autonomous eosinophil production with end organ or tissue complications (see Chapter 8).

Basophils are the least numerous blood leukocytes. Basophilic granules contain histamine, glycosaminoglycans, major basic protein, proteases, and a variety of other vasoactive inflammatory mediators. Basophils primarily function to activate the immediate (type 1) hypersensitivity responses. Increases in basophils are associated with hypersensitivity reactions including drug and food allergies. Basophilia has been reported with some chronic inflammatory diseases, such as tuberculosis, ulcerative colitis, and rheumatoid arthritis, but these reactions are quite rare. The most important association of basophilia is with myeloproliferative disorders, particularly chronic myeloid leukemia.

Monocytes and tissue histiocytes

Monocytes share their origin and functions with neutrophils. They are phagocytes, ingesting and killing microorganisms. Monocytes also may become the fixed phagocytic cells that

line portions of the circulation, particularly in the spleen and liver. In these tissues, they serve for the clearance of particulate matter, including microorganisms and effete blood cells, from the circulation. They are also an important source of the inflammatory cytokines (eg, tumor necrosis factor, interleukin 1, interferon-γ) that cause fever and many of the symptoms associated with infectious and inflammatory diseases. Monocytes can differentiate to tissue histiocytes, and these cells may then fuse to form giant cells, as occurs in tuberculosis and sarcoidosis. Alveolar macrophages in the lung, Kupffer cells in the liver, and osteoclasts and phagocytic cells in reticuloendothelial tissue are all forms of tissue histiocytes that are thought to derive from blood monocytes or, in some cases, from circulating monocyte progenitors. These phagocytic cells not only serve antimicrobial, scavenger, and secretory functions, they also participate in wound repair and antigen processing and presentation. Chronic inflammatory states may increase monocytes in the blood and the tissues. Transient monocytopenia occurs with stress and infections. In aplastic anemia and hairy cell leukemia, monocyte numbers are suppressed, but circulating monocyte counts and function are maintained in many other conditions that cause neutropenia. Inappropriate overstimulation of tissue macrophages, usually in the setting of infectious stimuli with or without underlying acquired or congenital immune dysregulation, may contribute to the sepsis-associated systemic inflammatory response syndrome (SIRS) and/or can lead to a severe pathologic disorder called "hemophagocytic syndrome" (see discussion later in the chapter).

Dendritic antigen-presenting cells

The major role of dendritic cells is the presentation of antigen to the immune system. Follicular dendritic cells in lymph nodes, Langerhans cells in the skin and other tissues, interdigitating dendritic cells in the thymus and lymph nodes, and reticular cells in the nodes and spleen all primarily function to process and present extracellular antigen in the context of class II major histocompatibility complex (MHC) molecules. Langerhans cells act locally, but they also migrate to lymphoid tissue where they present antigen and can serve as precursors to interdigitating dendritic cells. Langerhans cells and interdigitating dendritic cells are derived from the same progenitor that gives rise to blood monocytes and tissue histiocytes; however, their differentiation programs and surface immunophenotypic features are distinct (see Chapter 2). By comparison, follicular dendritic cells and reticular cells appear to arise from a mesenchymal cell progenitor. Dendritic cells take up exogenous antigen through macropinocytosis, Fc receptor-mediated internalization, and possibly other mechanisms. Class II-associated antigens on dendritic cells primarily bind to specific T lymphocytes. However, follicular dendritic cells in nodal germinal centers present antigen to B cells. Dendritic cells may serve as excellent vectors for tumor antigens. Thus, many research groups are isolating and expanding dendritic cell precursors *in vitro* to use in vaccine immunotherapy trials. An important pathologic condition of dendritic cells is Langerhans cell histiocytosis, an acquired clonal disorder that can lead to local or systemic tissue infiltration and organ failure (see discussion later in the chapter).

Mast cells

The origin and maturation pathway of tissue mast cells differ from those of basophils. Mast cells arise from a multipotent hematopoietic progenitor that is found in both the marrow and the peripheral blood. The progenitors migrate into the connective tissue of various organs where microenvironmental stem cell factor (SCF, also known as Kit ligand) stimulates mast cell differentiation through the c-Kit tyrosine kinase receptor (encoded by the *KIT* gene). Tissue mast cells may proliferate under certain conditions, and they appear to survive for weeks to months. The surface immunophenotype of mature mast cells overlaps, but is distinct from, blood basophils. Mature mast cell granules contain a number of vasoactive and immunoregulatory mediators, including tryptase, histamine, heparin, neutral proteases, hydrolases, prostaglandins, interleukins, and other inflammatory cytokines. Mast cells normally function as effector cells of immediate-type hypersensitivity, triggered through binding of IgE to the high-affinity receptor. Mast cells also degranulate after stimulation by complement mediators, certain cytokines, and drugs. Mast cells, like basophils, play a role in chronic inflammatory and allergic disorders, including allergic rhinitis, asthma, and anaphylaxis. Inappropriate nonatopic activity and overproduction of tissue mast cells occur in the group of disorders collectively referred to as mastocytosis (see discussion later in the chapter).

Neutrophilia

Clinical case

A 50-year-old businessman is seen because of knee and foot pain of 2 weeks' duration. Physical examination is normal, except for tenderness of the proximal metatarsal joint of the right first toe and swelling of the right knee. On further questioning, the practitioner learns the knee swelling may be due to a recent injury playing handball. Laboratory examination shows a white blood cell count of 18×10^9/L with an absolute neutrophil count of 16×10^9/L. Blood counts on previous annual physical examinations were normal.

Neutrophilia is defined as an absolute neutrophil count (ANC) more than 2 standard deviations above the mean or, in adults, greater than 7,700 neutrophils per microliter. Neutrophilia is associated with many different types of stress, including recent exercise, infection, and inflammatory diseases (Table 7-2). A prompt increase in the blood neutrophil count as well as the circulating levels of other leukocytes occurs with acute stress, exercise, anxiety (including visits to a physician), and epinephrine administration. Only rarely does this response more than double the count. It is attributable to demargination of cells, not to the release of cells from the marrow reserve. Normally about one half of the neutrophils in the circulation are loosely adherent to blood vessels and not counted in a routine blood count. These cells are described as being in the marginal pool. The other half of the neutrophils are circulating freely with the red cells and platelets. They are described as being in the circulating pool.

Neutrophilia associated with infections and inflammatory disorders occurs by 2 general mechanisms. First, during infection, a number of inflammatory cytokines are released into the circulation, inducing the release of mature neutrophils from the bone marrow. Second, the sustained cytokine response associated with infections may stimulate neutrophil production in the bone marrow. In contrast to neutrophil demargination, neutrophilia associated with infections and inflammatory disorders is marked by the presence of an increase in immature granulocytes in the blood, mostly comprising band forms but also including metamyelocytes and occasionally early granulocytic precursors. In addition, there often is a change in the morphology of neutrophils with the appearance of vacuoles and "toxic granulation," due to more intense staining of the primary granules of neutrophils. Cells released prematurely also may contain bits of endoplasmic reticulum, also called "Döhle bodies," which stain as blue bodies in the cytoplasm. In patients with neutrophilia, it is helpful to examine a blood smear to look for these changes.

Neutrophilia is also a feature of the myeloproliferative syndromes, particularly chronic myeloid leukemia (CML) and chronic neutrophilic leukemia (CNL). Other than molecular testing (Chapter 8), there are no diagnostic tests that will definitively distinguish reactive neutrophilia from a myeloproliferative disorder, but there are certain clinical features that are highly suggestive. Most important, in most cases of reactive neutrophilia, the inciting infection (or other stress) is usually clinically obvious and the neutrophilia is self-limited. In addition, the presence of splenomegaly,

Table 7-2 Causes of neutrophilia.

Acute neutrophilia	Chronic neutrophilia
Physical stimuli Cold, heat, exercise, convulsions, pain, labor, anesthesia, surgery	*Infections* Persistence of many infections that cause acute neutrophilia
Emotional stimuli Panic, rage, severe stress, depression	*Inflammation* Continuation of most acute inflammatory reactions, such as rheumatic fever, rheumatoid arthritis, gout, chronic vasculitis, myositis, nephritis, colitis, pancreatitis, dermatitis, thyroiditis, drug-sensitivity reactions, periodontitis, Sweet syndrome, familial periodic fever syndromes
Infections Many localized and systemic acute bacterial, mycotic, rickettsial, spirochetal, and certain viral infections	*Tumors* Gastric, bronchogenic, breast, renal, hepatic, pancreatic, uterine, and squamous cell cancers; rarely, Hodgkin disease, lymphoma, brain tumors, melanoma, and multiple myeloma
Inflammation or tissue necrosis Burns, electric shock, trauma, infarction, gout, vasculitis, antigen–antibody complexes, complement activation	*Drugs, hormones, and toxins* Continued exposure to many substances that produce acute neutrophilia; lithium; rarely, as a reaction to other drugs
Drugs, hormones, and toxins Epinephrine, etiocholanolone, endotoxin, glucocorticoids, venoms, vaccines, colony-stimulating factors	*Metabolic and endocrinologic disorders* Eclampsia, thyroid storm, overproduction of ACTH or glucocorticoids
Hereditary and congenital disorders Down syndrome, familial Mediterranean fever	*Hematologic disorders* Rebound from agranulocytosis or therapy of megaloblastic anemia, chronic hemolysis or hemorrhage, asplenia, myeloproliferative disorders, chronic idiopathic leukocytosis, LAD

Adapted from Dale DC. Neutropenia and neutrophilia. In: Williams WJ, et al., eds. Hematology. 6th ed. New York: McGraw-Hill; 2001:823–34.
ACTH = adrenocorticotropic hormone; LAD = leukocyte adhesion deficiency.

leukoerythroblastic features on the blood smear (tear drop and nucleated red blood cells), basophilia, or circulating promyelocytes or blasts are suggestive of a myeloproliferative disorder and may merit further evaluation. Finally, measurement of leukocyte alkaline phosphatase (LAP), which is high in reactive neutrophilia but usually low in CML, may be helpful. In the patient described previously, the uric acid level was high, leading to the diagnosis of gout as the cause of neutrophilia. This finding plus the neutrophilia initially raised concern about an underlying myeloproliferative disease. However, the absence of splenomegaly, a common feature of patients with CML, makes this possibility less likely.

In rare cases, neutrophilia may be due to intrinsic defects of neutrophil function. LAD and familial Mediterranean fever (FMF) are associated with neutrophilia; they are discussed in detail in the section on neutrophil function disorders.

Neutropenia

Neutropenia is defined as an ANC of less than 1500 cells per microliter. Of note, neutrophil levels are lower in some ethnic and racial groups, such as Africans, African Americans, and Yemenite Jews. For example, in adult African Americans the 95% confidence limits for the ANC are 1300–7400 cells per microliter. Neutropenia is classified based on the ANC as severe (<500/μL), moderate (500–1000/μL), or mild (1,000–1,500/μL). The risk of infection begins to increase with an ANC below 1,000/μL. Patients with neutropenia are prone to develop bacterial infections, typically caused by endogenous flora and involving mucous membranes, including gingivitis, stomatitis, perirectal abscesses, and cellulitis. Pneumonia and septicemia also occur, although less frequently. Fungal infections are less common, and there is no increased susceptibility to viral or parasitic infections.

Congenital or inherited neutropenia

The differential diagnosis of neutropenia is wide (Table 7-3). In this section, congenital syndromes associated with neutropenia and common causes of neutropenia are discussed. Recent studies have identified many of the genetic lesions responsible for congenital neutropenia (Table 7-4). Accordingly, genetic testing is now becoming an important diagnostic tool in the evaluation of patients with congenital neutropenia. The discussion of congenital neutropenia is focused on those syndromes in which neutropenia is the sole or major clinical feature. The bibliography contains several excellent reviews that include the congenital neutropenic syndromes shown in Table 7-4 that are not covered in this chapter.

Table 7-3 Causes of neutropenia.

Primary hematological disorders
Congenital/Inherited
Severe congenital neutropenia (Kostmann syndrome)
Cyclic neutropenia
Schwachman–Diamond syndrome
Neutropenia with congenital immunodeficiency diseases
Cartilage–hair hypoplasia syndrome
Diamond–Blackfan syndrome
Gricelli syndrome
Chédiak–Higashi syndrome
Barth syndrome
Pearson syndrome
Familial benign neutropenia
WHIM syndrome and myelokathexis
Dyskeratosis congenita
Acquired
Acute leukemia
Myelodysplastic syndromes
Chronic lymphocytic leukemia
Hodgkin disease
Non-Hodgkin lymphoma
Aplastic anemia
Chronic idiopathic neutropenia
Nutritional deficiencies: copper, vitamin B_{12}, folic acid
Secondary disorders
Immune neutropenias
Alloimmune neutropenia
Isoimmune neutropenia
Autoimmune neutropenia
Neutropenia with autoimmune diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Felty syndrome
Sjögren syndrome
Neutropenia with clonal large granular lymphocytosis
Neutropenia with splenomegaly
Neutropenia with infectious diseases
Sepsis
Rickettisal: human granulocytic ehrlichiosis
Viral: mononucleosis, parvovirus, HIV
Drugs
Dose and exposure related
Idiosyncratic

Adapted from Dale DC, Liles WC. Neutrophils and monocytes: normal physiology and disorders of neutrophil and monocyte production. In: Handin RI, Lux SE, Stossel TP, eds. Blood: Principles and Practice of Hematology. Philadelphia: Lippincott Williams & Wilkins; 2002.

Table 7-4 Genetic causes of congenital neutropenia.

Syndrome	Genetics
Severe congenital neutropenia	*ELA2* (sporadic and AD[a]); *GFI1*, *CSF3R* (*AD*); *WAS*(XL)
Kostmann syndrome[b]	Unknown
Cyclic neutropenia	*ELA2*
WHIM syndrome/myelokathexis	*CXCR4*
Shwachman–Diamond syndrome	*SBDS*
Barth syndrome	*TAZ*
Glycogen storage disease type Ib	*G6PT1*
Chédiak–Higashi syndrome	*LYST*
Griscelli syndrome	*MYO5A, RAB27A, MLPH*
Cartilage–hair hypoplasia	*RMRP*
Pearson syndrome	variable mitochondrial DNA deletions
Dyskeratosis congenital	*DKC1 (XL); TERC (AD)*
Neutropenia associated with primary immunodeficiency	
Hyper IgM syndrome	*HIGM1, IKBKG(XL), AICDA(AR)*
X-linked agammaglobulinemia	*BTK(XL)*

[a]AD = autosomal dominant; AR = autosomal recessive; XL = X-linked.

[b]Kostmann syndrome typically refers to the autosomal recessive form of severe congenital neutropenia first described by Kostmann.

Severe congenital neutropenia (Kostmann syndrome)

Clinical case

A 2½-week-old infant has had persistent neutropenia since birth. Because of fever during the first week of life, he had several blood counts. One ANC was 0.9 × 10^9/L, but all other counts were 0.0–0.2 × 10^9/L. He now has neutropenia, monocytosis, and thrombocytosis, but is doing well without infection. On marrow examination, there is "maturation arrest" at the myelocyte stage. There are almost no metamyelocytes, bands, or mature neutrophils in the marrow. The appearance of the erythroid cells, lymphocytes, and megakaryocytes is normal.

Severe congenital neutropenia (SCN) is a heterogeneous group of disorders first described in an extended consanguineous family by the Swedish physician Rolf Kostmann. The disease has thus also been known as Kostmann syndrome, although this eponym has been used to define a subset of patients with autosomal recessively inherited SCN. SCN is characterized by severe neutropenia present at birth with ANCs generally below 200 cells per microliter. The bone marrow invariably shows an arrest in myeloid maturation with an accumulation of promyelocytes or myelocytes. Other hematological parameters are generally normal, although peripheral monocytosis and increase in bone marrow eosinophils is often observed.

SCN demonstrates multiple modes of inheritance, including autosomal recessive, autosomal dominant, X-linked, and sporadic patterns. Accordingly, recent genetic studies have identified multiple gene mutations in SCN, including *ELA2*, *GFI1*, *CSF3R*, and *WASP*. By far the most common mutations affect the *ELA2* gene encoding neutrophil elastase with reported frequencies of 35–88% (all in autosomal dominant or sporadic SCN). To date, 47 different, mostly missense, *ELA2* mutations have been identified in patients with SCN. No consistent effect of these mutations on neutrophil elastase function has been described; thus, the molecular pathogenesis remains unclear.

Historically, affected patients had a poor prognosis and often succumbed in the first or second decade of life with recurrent severe bacterial infections. The use of G-CSF has changed the natural history of this disease; the results of a randomized phase III trial comparing G-CSF with no treatment in patients with SCN demonstrated that the majority (>90%) of patients had a significant increase in circulating levels of neutrophils and reduction in the incidence and severity of bacterial infections. There is substantial patient-to-patient variability in the dose of G-CSF that is required to achieve an acceptable neutrophil count, with some children requiring only 1–2 μg/kg on alternate days and others responding only to doses of 25–50 μg/kg/d. Recognized adverse effects of chronic G-CSF therapy include splenomegaly, bone pain, vasculitis, and osteoporosis.

With longer survival and close observation, it has become clear that CN is a preleukemic disorder. A recent update of the severe chronic neutropenia international registry showed that the cumulative incidence of myelodysplastic syndrome (MDS) or AML was 21%. The hazard rate for AML/MDS increases with the time, reaching 8% per year rate in patients on G-CSF therapy for 12 years. Patients less responsive to G-CSF (defined as an ANC of <2,188/μL after 6 months of

treatment) are at the highest risk of developing AMD/MDS, with a cumulative risk at 10 years of 40%. It should be emphasized that there is no definitive proof that G-CSF directly contributes to leukemic transformation. Indeed, reports of AML/MDS in SCN predate the use of G-CSF. Moreover, myeloid malignancies are rare in children and adults with cyclic neutropenia despite many years of G-CSF treatment (see discussion later in the chapter). Thus, the contribution of G-CSF to the development of AML/MDS in patients with SCN remains controversial, and therapy with G-CSF should not be withheld from newly diagnosed patients on this basis. Additional studies have addressed the molecular lesions that are associated with transformation to MDS/AML in patients with SCN. The most fascinating of these is the acquisition of somatic mutations in the G-CSF receptor, which truncate the carboxy terminus. Monosomy 7 is also common in the bone marrows of patients with MDS and AML, and some cases also show *RAS* mutations. Based on the risk of leukemic transformation in SCN, patients should receive the lowest dose of G-CSF that is required to maintain an acceptable neutrophil count and should undergo yearly bone marrow examinations with cytogenetic analysis.

Hematopoietic stem cell transplantation (HSCT) from an HLA-identical sibling is curative for patients with SCN who are refractory to G-CSF treatment. A more difficult question involves when to perform transplantation in SCN patients who are doing well on G-CSF and have an HLA-matched sibling donor. The limited published data indicate that transplant cures a high percentage of patients with neutropenia only, but is usually ineffective in children who have progressed to MDS/AML. Patients who acquire a G-CSF receptor mutation or are less responsive to G-CSF (see previous description) appear to have an elevated risk of developing MDS or AML, and this may prove useful for identifying children who should be transplanted. However, no prospective data exist that address this question. HSCT from unrelated donors is not recommended for patients with SCN who are doing well on G-CSF treatment.

Cyclic neutropenia

Clinical case

A 2½-year-old boy is seen because of frequent fevers, mouth sores, and treatment of recurrent pharyngitis and otitis. The symptoms occur about every 3 weeks. The patient's mother had similar problems as a child, which seemed to get better in her late teenage years. The patient has a temperature of 38.7°C with inflamed gingivae and a large ulcer on the tip of his tongue. Cervical lymph nodes are enlarged; the abdomen is slightly tender. The rest of the examination is normal. The white blood cell count is 3.5×10^9/L, and the ANC is 0.

Cyclic neutropenia (CN) is a disorder of granulopoiesis characterized by 21-day oscillations in the number of circulating neutrophils. In CN patients, neutrophil counts often fluctuate between normal or near normal levels to less than 200/μL. The diagnosis of CN should be considered in patients with recurrent fever, mouth sores, and upper respiratory infections. Usually these symptoms recur at regular 3-week intervals. CN is diagnosed by serial blood counts. The "up" time of neutrophils is usually much shorter than the "down" time. Therefore, counts 2 or 3 times per week for at least 6 weeks are required to be sure of the diagnosis. CN is usually diagnosed as a sporadic or (in roughly one third of cases) an autosomal dominantly inherited disorder in young children who were healthy at birth, but soon thereafter begin to have recurrent respiratory illnesses. These children may be treated as having recurrent viral or bacterial infections before serial complete blood counts (CBCs) are performed. The differential diagnosis in this case includes CN, SCN, autoimmune neutropenia, and idiopathic neutropenia. Rare acquired cases of adult-onset CN (or cyclic hematopoiesis) have been reported in association with clonal T-lymphocyte disorders, Crohn disease, pregnancy, and exposure to radiation or certain drugs.

Though not required to make the diagnosis, serial marrow examinations in CN show periodic interruptions of cell production, with arrest of development at the promyelocyte stage during the first days of severe neutropenia with each cycle. Over the next few days, hematopoietic recovery occurs with appearance of a complete complement of cells of the neutrophil lineage.

Recent genetic studies have identified mutations of the *ELA2* gene in nearly all patients with CN. Consequently, genetic testing for *ELA2* mutations is a valuable diagnostic tool. As noted previously, *ELA2* mutations also are found in the majority of patients with SCN, suggesting that CN and SCN are related and fall along a continuum of disorders of granulopoiesis. Interestingly, the amino acid substitutions identified in patients with CN are, for the most part, distinctive from those found in patients with SCN.

CN is now treated with daily or alternate-day G-CSF, which largely eliminates the periodic fevers, mouth ulcers, and most of the other inflammatory complications associated with this disease. In contrast to SCN, there is no evidence of an increased risk of MDS or AML in patients with CN. In many children the cyclic pattern evolves to a state of chronic, persistent neutropenia.

Shwachman–Diamond Syndrome

Shwachman–Diamond syndrome (SDS) is a rare multisystem disorder characterized by exocrine pancreatic insufficiency, bone marrow dysfunction, and skeletal abnormalities. Bone marrow dysfunction is present in nearly all patients

with SDS. In the largest series, 86 of 88 patients with SDS displayed chronic or intermittent neutropenia. Moreover, defects in neutrophil function, most notably impaired chemotaxis and motility, have been reported. Anemia and thrombocytopenia, though less common, are present in more than a third of patients. Defects in B- and/or T-lymphocyte function also have been described. Similar to SCN, patients with SDS have a marked propensity to develop MDS or AML. A recent series of 21 patients with SDS showed that the overall risk of MDS/AML was 24%. SDS is the second most common cause of congenital exocrine pancreatic insufficiency (behind cystic fibrosis). Maldigestion caused by pancreatic insufficiency is present in nearly all patients in early life but improves with increasing age in most patients. Bony abnormalities are common with rib cage abnormalities and metaphyseal dysostosis the most common features. Growth retardation also is common in SDS patients, but it is not thought to be secondary to malnutrition.

SDS is inherited in an autosomal recessive fashion. Recent studies have identified compound heterozygous mutations of the *SBDS* gene in approximately 90% of patients with SDS. Thus, genetic testing for SBDS mutations is a valuable diagnostic tool for SDS. The SBDS gene encodes for a protein of unknown function; hence, mechanisms of disease pathogenesis remain unclear.

Treatment of SDS includes pancreatic enzyme replacement and fat-soluble vitamins for pancreatic insufficiency. Neutropenia is usually treated with G-CSF. Stem cell transplantation is generally reserved for patients with bone marrow failure or who have transformed to AML/MDS. A recent study reported 5-year event-free survival of 60% in patients with SDS following stem cell transplantation.

WHIM syndrome

WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome is a rare inherited disorder characterized by neutropenia, hypogammaglobulinemia, and extensive human papillomavirus (HPV) infection. Affected individuals typically present with recurrent bacterial infections from birth with ANCs of less than 1000/μL. Despite the peripheral neutropenia, the bone marrow of affected patients is generally hypercellular with increased numbers of mature neutrophils (a condition termed "myelokathexis). Patients commonly have lymphopenia or T-cell dysfunction, yet immunity to most viral pathogens is normal. The major exception is human papillomavirus, which is the cause of warts in patients with WHIM syndrome. Although some patients have few if any warts, the majority of patients suffer from extensive verrucosis. They typically appear in the first or second decades of life and can involve any mucocutaneous surface. Hypogammaglobulinemia is variable, ranging from normal to modestly decreased serum IgG, IgM, and IgA. Treatment with G-CSF or GM-CSF is effective in correcting the neutropenia.

The majority of patients with WHIM syndrome have heterozygous mutations of the *CXCR4* gene. CXCR4 is a G-protein–coupled heptahelical receptor that is the major receptor for SDF-1 or CXCL12. There is convincing evidence that SDF-1/CXCR4 signaling is a key regulator of neutrophil release from the bone marrow. Specifically, SDF-1/CXCR4 provides a signal to retain neutrophils in the bone marrow. The mutations of *CXCR4* in WHIM syndrome truncate the carboxy-terminal (cytoplasmic) tail, resulting in enhanced CXCR4 signaling. These observations support the current model in which enhanced signaling by the *CXCR4* mutants in WHIM syndrome leads to abnormal neutrophil retention in the bone marrow.

Chédiak–Higashi syndrome

Chédiak–Higashi syndrome (CHS) is a rare inherited syndrome characterized by partial albinism, a mild bleeding diathesis, severe immunodeficiency, and progressive neurologic defects. The pathognomonic feature of CHS is the presence of giant inclusion bodies in virtually all granulated cells, particularly neutrophils. Neutropenia is common, and the residual neutrophils display functional defects. Approximately 85% of patients will progress to an "accelerated phase" characterized by a nonclonal lymphohistiocytic infiltration of multiple organs, leading to multiorgan system failure. CHS is inherited in an autosomal recessive fashion and is due to mutations of the *LYST* gene. The loss of LYST protein disrupts the normal regulation of secretory lysosomes leading to hypopigmentation and dysregulated immune cell function. Secretory lysosomes are modified lysosomes that undergo regulated secretion. They are present in many different cell types, including melanocytes, platelets, neutrophils and other cells of the immune system. Other than allogeneic bone marrow transplantation, treatment is largely supportive.

Neonatal alloimmune neutropenia

Physiological and acquired neutropenia in premature infants, including idiopathic or immune causes, are much more common than inherited/congenital neutropenia. In alloimmune neonatal neutropenia, there is transplacental transfer of maternal IgG directed against paternal antigens expressed on neonatal neutrophils. It is analogous to neonatal erythroblastosis secondary to Rh incompatibility. Rarely, the maternal antibody is secondary to autoimmune neutropenia in the mother. The incidence has been estimated at 2 per 1,000 live births. The bone marrow usually shows normal cellularity with a late myeloid arrest. Maternal alloimmunization

probably occurs during the first trimester of pregnancy. Only some of the antigens provoking this response are known. Two antigens known to be responsible for this syndrome, NA1 and NA2, originally described by Lalazari, are now known to be isotypes of CD16 or FCγRIII. These children may develop omphalitis or skin infections; however, they are also at risk for severe life-threatening infections. Aggressive antibiotic therapy must be given for documented infection, and recombinant G-CSF should be considered, although the response is variable and unpredictable. With supportive care, the neutropenia usually spontaneously resolves within 3 to 28 weeks (average of 11 weeks). Overall, the prognosis for infants with alloimmune neutropenia syndrome is generally quite favorable.

Primary autoimmune neutropenia

Primary autoimmune neutropenia (AIN; also termed "chronic benign neutropenia of infancy and childhood") typically occurs in children between the ages of 5 to 15 months but can be present from 1 month through adulthood. The ANC is typically between 500 and 1000/μL. Serious infections are infrequent and may reflect the ability of patients to raise their neutrophil counts during acute illnesses. Bone marrow examination is rarely indicated. When performed, it reveals minimal abnormalities or only a deficit of mature neutrophils. Spontaneous remission occurs in most patients. In the largest series, 95% of 240 patients with AIN had a spontaneous remission, usually within 24 months of diagnosis. The pathogenesis is thought to be immune-mediated neutrophil clearance. Indeed, in the great majority of published cases, antibodies to neutrophil antigens can be detected, though multiple blood samples may need to be analyzed. Antibodies directed against FCγRIII or CDllb/CD18[4] (also termed the "type 3 complement receptor") are the most common detected. Many patients remain free of infections, and no specific therapy is required. For those patients with recurrent infections, prophylactic antibiotics or intermittent treatment with G-CSF may be indicated. Though rarely needed, high-dose intravenous immunoglobulin and/or corticosteroid therapy have been reported to be effective.

Secondary autoimmune neutropenia

Neutropenia is occasionally associated with autoimmune disease, most commonly rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Sjögren syndrome. Moreover, there is a strong association of neutropenia with large granular lymphocyte leukemia (LGL) often in association with RA. LGL is discussed in a separate section later in the chapter. In SLE, neutropenia occurs in approximately 50% of patients. The neutropenia is generally mild, has little impact on disease, and requires no specific treatment. The pathogenesis of neutropenia in SLE is unclear. Neutrophil antibodies have been implicated but are present in some SLE patients without neutropenia; thus, the clinical utility of measuring antineutrophil antibodies in SLE is questionable. Of note, sera samples from a portion of neutropenic patients with SLE contain anti-SSA/Ro or anti-SSB/La antibodies with potent binding and functional activity against neutrophils; however, the clinical relevance and applicability of these findings await further confirmatory studies. As with SLE, the differential diagnosis for neutropenia in RA is wide, and drug-induced neutropenia must be considered. Felty syndrome is defined as the triad of unexplained neutropenia, long-standing RA, and variable splenomegaly. There is an increased risk of infections in these patients. Treatment is usually directed at the underlying RA.

Large granular lymphocyte leukemia

Clinical case

A 60-year-old female presents with fatigue and arthralgias. She has recurrent fevers and complains of upper respiratory infections but has not had documented bacterial infections. On examination, there is no lymphadenopathy or splenomegaly. A CBC shows the following: hematocrit 35%, platelets 225 × 10^9/L, white blood cell (WBC) 3.5 × 10^9/L, ANC 0.2 × 10^9/L. Peripheral blood smear shows frequent large lymphocytes with azurophilic granules.

This case is suggestive of LGL, a clonal disorder of cytotoxic T lymphocytes or natural killer (NK) cells. Discussion here is limited to T-cell LGL (TLGL) because it is most strongly associated with severe chronic neutropenia. TLGL is a disease of older patients (median age of 60) that is associated with RA in 25% of cases. Patients often present with unexplained neutropenia. Increased numbers of large lymphocytes with abundant cytoplasm and azurophilic granules are often, but not always, apparent on examination of the blood smear. Splenomegaly is present in 25–50% of patients. The diagnosis is based on the finding of an elevated number of LGL cells ($CD3^+$, TCR^+, $CD4^-$, $CD8^+$, $CD57^+$) by flow cytometry in blood or bone marrow concurrent with evidence of T-cell clonality. Neutropenia is present in 85% of patients and is often severe (50% with an ANC of less than 500/μL). The pathogenesis of neutropenia in TLGL is the subject of intense study. Current models suggest that increased peripheral destruction of neutrophils secondary

to immune complexes and bone marrow suppression of granulopoiesis via Fas ligand secretion contribute to the neutropenia. TLGL typically has an indolent but chronic course with median survival of greater than 10 years. In the absence of symptomatic cytopenia, no treatment is required. The most common indication for therapy is recurrent infection secondary to neutropenia. A wide variety of therapeutic interventions have been used in TLGL, and standard therapy remains undefined. It is most commonly managed with immunosuppressive agents including methotrexate, cyclosporine, glucocorticoids, or G-CSF.

Nonimmune chronic idiopathic neutropenia

In a subset of patients with chronic neutropenia, there is no evidence of immune-mediated disease. The diagnosis of nonimmune chronic idiopathic neutropenia in adults (NI-CINA) is based on the presence of chronic acquired neutropenia in the absence of underlying autoimmune disease, cytogenetic abnormality, antineutrophil antibodies, or other obvious explanation for neutropenia. In addition to neutropenia, lymphopenia, monocytopenia, anemia, or thrombocytopenia are occasionally seen. Bone marrow findings are highly variable, with both hyperplastic and hypoplastic bone marrow cellularity reported. The pathogenesis of NI-CINA is poorly understood, though it has been suggested that chronic low-grade inflammation may contribute. Fortunately, the clinical course is usually benign, infections infrequent, and specific treatment not required.

Neutropenia due to idiosyncratic drug reactions

Clinical case

A 50-year-old teacher with a history of ulcerative colitis for 1 year presents to the emergency room with fever, chills, and sore throat for 24 hours. On examination, the temperature is 39.6°C, blood pressure 90/60, pulse 105, and respiratory rate 28. The patient is confused and reports that her throat is very sore. The abdomen is slightly tender, and bowel sounds are absent. Based on the patient's presentation, therapeutic measures for septic shock are initiated. Within a few minutes, a CBC reveals a WBC of 1.5×10^9/L with an ANC of 0. On questioning of the patient's husband, you learn that she had been in her usual state of health until a few days ago. She has had long-standing complaints of chronic diarrhea with intermittent blood and mucous in the stool. Her only medication is sulfasalazine begun about 3 months ago.

Drug-induced agranulocytosis is a serious medical problem, with an estimated frequency of 1 per 1.6–7 million and a case fatality rate of approximately 10%. Though certain medications carry a higher risk of agranulocytosis (Table 7-5), it is probably wise to consider most medications as potential offenders, thus emphasizing the need for a careful drug history in all patients who present with acquired neutropenia. Among general medical adult patients, antibiotics, antithyroid drugs, antiplatelet agents, psychotropic drugs, and nonsteroidal anti-inflammatory agents are the medications most commonly associated with agranulocytosis. In most cases, agranulocytosis presents within 6 months, and usually within 3 months, after starting the offending drug. The clinical presentation of drug-induced agranulocytosis is often less dramatic than in this case, but patients often have fever and pharyngitis as their first symptoms. Sepsis and/or pneumonia may occur in 10 to 30%. Usually the prognosis is good because neutrophil counts recover within about a week if the offending medication is withdrawn. The disease mechanism is often unclear. In some well-studied cases, the offending drug serves as a hapten in association with an endogenous protein, probably an antigen expressed on the neutrophil surface. The immune response to this complex results in neutrophil destruction, severe neutropenia, and susceptibility to infection. Other drugs may impair production of neutrophils by a direct toxic effect on myeloid precursors.

Drug induced agranulocytosis is difficult to anticipate. Serial blood counts are now recommended for patients on some drugs, such as sulfasalazine, clozapine, phenothiazines, and antithyroid drugs, because of the relatively high frequency of drug-induced neutropenia associated with these agents. Practices are not standardized, however, and the benefit of frequent blood counts is not established.

Management includes prompt withdrawal of all potentially offending drugs and administration of broad-spectrum antibiotics, usually with inpatient management. The mean time to recovery is approximately 10 days, but the duration of neutropenia is highly variable. Therapy with hematopoietic growth factors, particularly G-CSF, is controversial. A number of nonrandomized trials have reported a shortened duration of neutropenia, less antibiotic use, and reduced hospital stay with the use of G-CSF. Bone marrow examination is usually not necessary in cases with otherwise normal hematocrit, platelet count, and red cell morphology. The time to hematological recovery may be proportional to the severity of the marrow defect; that is, if no cells at the myelocyte stage are seen on an aspirate sample, it will probably be several days before recovery occurs. Overall survival is approximately 95%. A neutrophil count $< 0.1 \times 10^9$/L and the presence of sepsis or severe infection are associated with delayed neutrophil recovery.

Table 7-5 Major drugs associated with agranulocytosis.

Anti-inflammatory agents	*Antibiotics*
Indomethacin*	Sulfomamides*
Gold salts*	Cephalosporins
Sulfasalazine*	β-lactam antiobiotics*
Penicillamine	Chloramphenicol*
Diclofenac*	Clindamycin
Phenacetin	Gentamycin*
Dipyrone*	Trimethoprim-sulfamethoxazole*
Oxyphenbutazone*	Tetracyclines
Phenylbutazone*	Vancomycin
Cardiovascular agents	Rifampin
Ticlopidine*	Streptomycin
Spironolactone*	Isoniazid
Thiazide diuretics	Erythromycin*
Furosemide	Rifabutin
Acetazolamide	Imipenem
Dipyridamole*	*Antithyroid agents**
Hydralazine	Carbimazole
Propranolol*	Methimazole
Captopril*	Propylthiouracil*
Enalopril	*Pyschotropic agents*
Quinidine	Risperidone
Tocainide	Chlorpromazine
Procainamide*	Clozapine*
Methyldopa*	Olanzapine
Anticonvulsants	Phenothiazines
Carbamazepine*	Meprobamate
Valproic acid	Benzodiazepines
Ethosuximide	*Hypoglycemic agents*
Phenytoin*	Chlorpropamide
Antidepressants	Tolbutamide
Amitriptyline	Glyburide*
Amoxapine	*Antifungal agents*
Desipramine	Amphotericin B
Doxepin	Flucytosine
Imipramine	*Other agents*
Clomipramine*	Allopurinol
Antimalarials	Levamisole
Chloroquine	Colchicine
Dapsone*	Riluzole
Pyrimethamine	Cimetidine*
Quinine	Ranitidine

*More frequently reported to cause neutropenia in epidemiologic studies.
Note: Documentation of the role of specific drugs in the causation of neutropenia is dependent on (i) the frequency of the occurrence among patients, (ii) the timing of the event in relationship to drug use, (iii) the absence of alternative explanations, or (iv) the inadvertent or intentional reuse of the drug (rechallenges) with a similar response. Readers who require supplementary lists of putative drugs involved in the development of neutropenia or wish to read original references for these interactions are referred to Kaufman DW, et al. The international agranulocytosis and aplastic anemia study. Risks of agranulocytosis and aplastic anemia. JAMA. 1986;256:1749; Roeser HP. Drug–bone marrow interactions. Med J Austral. 1987;146:145; Kaufman DW. Drugs in the etiology of agranulocytosis and aplastic anaemia. Eur J Haematol. 1996;60(Suppl):23; Ibanex L, et al. Population-based drug-induced agranulocytosis. Archives of IM. 2005;165:869. Adapted from Dale DC. Neutropenia and neutrophilia. In: Williams WJ, et al., eds. Hematology. 6th ed. New York: McGraw-Hill; 2001:823–34.

Chemotherapy-induced neutropenia

Clinical case

A 65-year-old woman with stage III multiple myeloma, is treated with vincristine, adriamycin, and dexamethasone using a tunneled central venous catheter. About 7 days after the initial course of therapy, she develops fever, chills, and rigors and is admitted to the hospital with presumed sepsis. The hematocrit is 32%, platelet count is 25×10^9/L, WBC is 1.3×10^9/L, and the ANC is 0.03×10^9/L. She is initially treated with broad-spectrum antibiotics. Blood cultures are positive for *Staphylococcus aureus*, probably due to infection via an intravenous catheter.

Chemotherapy-induced neutropenia is a common complication of the treatment of cancer. The risk of life-threatening infections increases substantially with neutrophil counts less than 500/μL. Risk increases with the duration of neutropenia, increasing age, and the coexistence of other severe illnesses. In this case, the presence of an intravenous catheter provided a route for serious infection to occur. Chemotherapy-induced neutropenia occurs with a wide range of myelotoxic drugs and treatment regimens. In current practice, the occurrence of fever in a patient with severe chemotherapy-induced neutropenia is an indication for hospitalization with immediate initiation of broad-spectrum antibiotics pending culture results. Evidence-based guidelines for the indications and use of antibacterial, antifungal, and antiviral agents in patients with neutropenia and cancer were published by the Infectious Diseases Society of America (Hughes et al., 2002; also see commentary by Rolston, 2004). The reader is referred to these documents for specifics regarding prophylaxis and treatment of neutropenic patients. Prophylactic use of hematopoietic growth factors should be considered after chemotherapy in elderly patients and in other patients with clinical features that place them at significant risk of complications from infectious diseases. Either G-CSF or GM-CSF could be used because they have equivalent efficacy and outcome in this setting. However, the benefits, although statistically significant, are only modest. Evidence-based clinical practice guidelines for the prophylactic and therapeutic use of hematopoietic colony-stimulating factors in patients with cancer or hematologic malignancies have been published by the National Comprehensive Cancer Network (Crawford et al., 2005), the American Society of Clinical Oncology (Ozer et al., 2000), and by the Hemato-Oncology Task Force of the British Committee for Standards in Hematology (Pagliuca et al., 2003). This subject is also reviewed in Chapter 3 (Hematopoietic Growth Factors and Cytokines).

Key points

- Neutrophilia and neutropenia are very common myeloid changes in response to inflammatory, infectious, and malignant diseases.
- Transient neutropenia is not uncommon in infants and children, and may be due to infection, auto- or alloimmune mechanisms, unidentified causes (ie, idiopathic), or, less commonly, genetic disorders of granulopoiesis.
- The genetic basis for many congenital neutropenia syndromes has been identified, and genetic testing is becoming an important diagnostic tool in the evaluation of patients with chronic neutropenia.
- Cyclic neutropenia and many cases of congenital neutropenia are associated with mutations of *ELA2*, the gene encoding for neutrophil elastase. Treatment with G-CSF improves neutrophil counts and prevents clinical infections; however, patients with congenital neutropenia must be monitored for evolution to MDS or AML.
- Neutropenia in adults is frequently due to drugs, both as a predictable response to myelotoxic agents and as an idiosyncratic reaction to almost any drug. Less commonly, neutropenia is due to infection, acquired hematopoietic disease, autoimmune disorder, or a clonal proliferation of LGLs.

Disorders of neutrophil function

Clinical case

A 2-year-old boy has had recurrent furuncles and deep abscesses since the first few months of life. On examination there is no active infection, but there are scars from drainage of previous abscesses. CBC shows a hematocrit of 32%, WBC is 12×10^9/L, and the platelet count is 400×10^9/L. The differential count is normal, and the morphology of the leukocytes is normal. The IgG level is increased; the levels of IgM and IgA are normal.

Recurrent fevers, otitis media, and sinopulmonary infections are common in young children, and it may be difficult to assess when a child has had "too many" infections and requires a careful workup. However, there are certain conditions that should raise concern for an underlying immunodeficiency syndrome, including neutrophil function disorders, and may merit further evaluation. These include (i) recurrent systemic bacterial infections (eg, sepsis, osteomyelitis, meningitis), (ii) infections at unusual sites (eg, hepatic or brain abscess), (iii) recurrent bacterial infections (eg, pneumonia, sinusitis, cellulitis, lymphadenitis, draining otitis media), (iv) infections caused by unusual pathogens (eg, *Aspergillus* pneumonia, disseminated candidiasis, *Serratia marcescens*, *Nocardia* sp, *Burkholderia cepacia*), and (v) chronic gingivitis or recurrent aphthous ulcers (modified from Boxer, 2003). In the case described previously, the history of recurrent abscesses and a normal ANC would merit further evaluation for a neutrophil function disorder. The most widely known disorders with abnormalities of neutrophil function are described below.

Myeloperoxidase deficiency

Myeloperoxidase (MPO) deficiency is the most common disorder of phagocytes, with 1 in 4,000 individuals having a complete deficiency of MPO. It is inherited in an autosomal recessive fashion and is due to mutations of the MPO gene. MPO is a primary granule enzyme that catalyzes the conversion of H_2O_2 to hypochlorous acid and other toxic intermediates that greatly enhance polymorphonuclear (PMN) microbicidal activity. The diagnosis can be made with histochemical assays for MPO on neutrophils. Of note, most patients (95%) with MPO deficiency are asymptomatic. An increase in mucocutaneous infections with *Candida* strains has been reported, particularly in patients with concurrent diabetes mellitus. There is no specific treatment.

Leukocyte adhesion deficiency

LAD is a rare disorder manifested by delayed wound healing, recurrent bacterial infections, and neutrophilia. There are 2 distinct forms of LAD. In LAD-1, mutations of *ITGB2*, encoding the β_2-integrin (CD18) chain, disrupt β_2-integrin function. In LAD-2, mutations of *FUCT2*, encoding GDP-fucose transporter-1, disrupt the generation of ligands on neutrophils required for selectin binding. Both mutations result in severely impaired neutrophil chemotaxis and emigration from the blood to sites of infection. Patients with LAD-2 also display short stature, abnormal facies, and severe cognitive impairment. A history of consanguinity may be an important clue in evaluating children for LAD. Definitive treatment of LAD requires allogeneic HSCT, though there is a single case report suggesting that fucose treatment may be efficacious in patients with LAD-2.

Hyperimmunoglobulin E syndrome

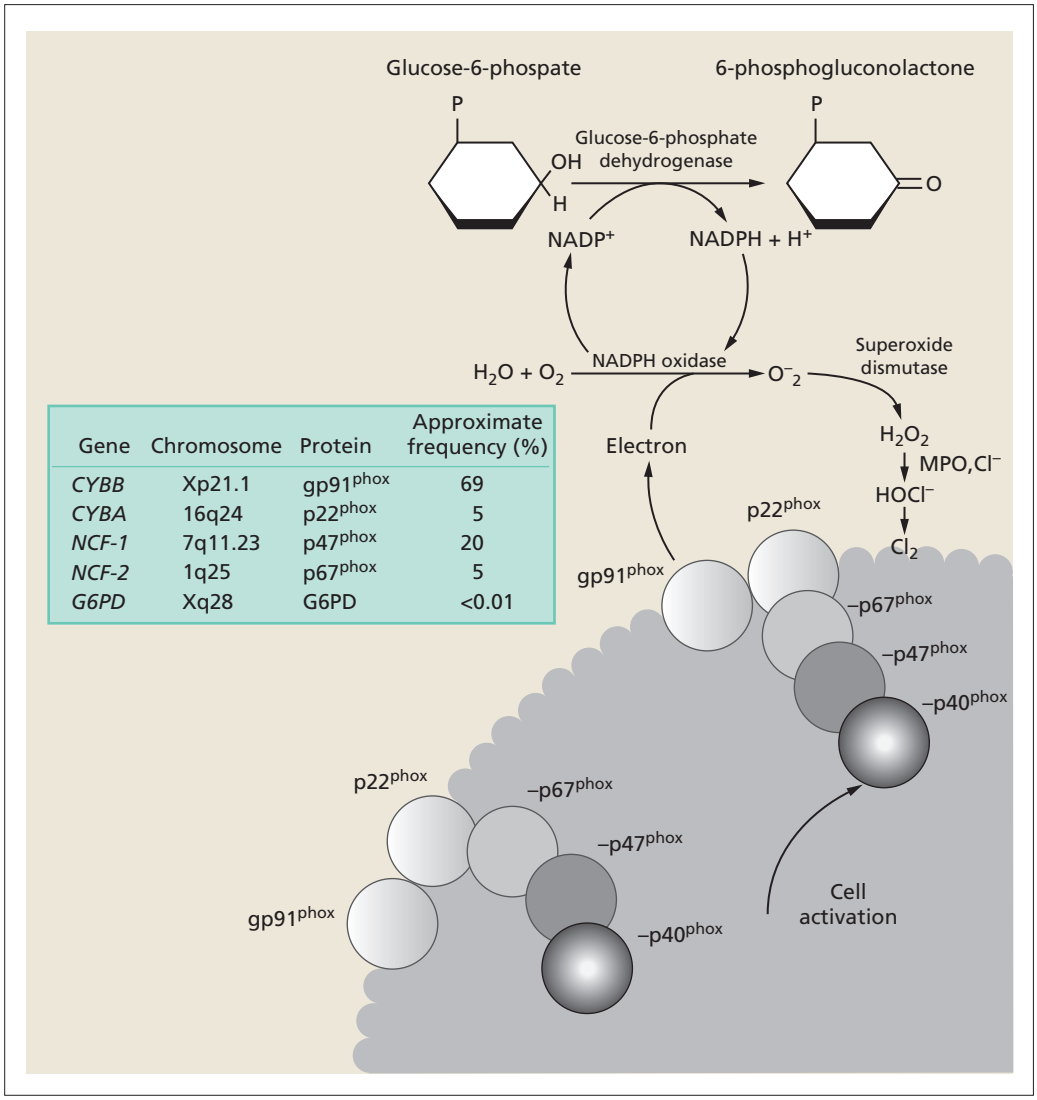
Hyperimmunoglobulin E syndrome (previously known as Job syndrome) is manifested by defective neutrophil chemotaxis, recurrent bacterial infections (typically involving the skin, sinuses, or lung), mucocutaneous infections with *Candida albicans*, and elevated serum IgE levels. Patients may also present with a pruritic dermatitis in the first few weeks of life. Associated features that might aid in the diagnosis include coarse facial features, recurrent fractures, and short stature. The genetic basis of this syndrome is currently unknown, and there is no specific treatment.

Neutrophil-specific granule deficiency

Neutrophil-specific granule deficiency is a rare disorder also associated with recurrent severe skin and lung infections caused by *S. aureus*, *S. epidermidis*, and gram-negative bacteria. These patients' neutrophils are morphologically abnormal; that is, they are devoid of specific granules but contain normal azurophilic granules, and they do not migrate normally in response to chemotactic stimuli. This syndrome is due to loss-of-function mutations of CCAAT/enhancer-binding protein ε (C/EBPε).

Chronic granulomatous disease

The most frequent manifestations of chronic granulomatous disease (CGD) are cutaneous and pulmonary infections and severe facial acne. In the lymph nodes and other tissues, granulomatous inflammatory responses develop. This disorder is due to mutations in one of the components of the NADPH oxidase system that results in a failure to generate the oxidative burst that normally produces reactive oxygen species and the bactericidal agent, hypochlorous acid, within the neutrophil (Figure 7-2). Roughly two thirds of CGD



Gene	Chromosome	Protein	Approximate frequency (%)
CYBB	Xp21.1	gp91^{phox}	69
CYBA	16q24	p22^{phox}	5
NCF-1	7q11.23	p47^{phox}	20
NCF-2	1q25	p67^{phox}	5
G6PD	Xq28	G6PD	<0.01

Figure 7-2 Relation among the components of NADPH oxidase that are affected in patients with chronic granulomatous disease. The membrane-bound phagocyte oxidase components, the 91-kd glycoprotein (gp91^{phox}) and the 22-kd protein (p22^{phox}), interact with the cytoplasmic components, the 47-kd protein (p47^{phox}) and 67-kd protein (p67^{phox}). Glucose-6-phosphate dehydrogenase (G6PD) converts glucose-6-phosphate to 6-phosphogluconolactone, generating NADPH and a hydrogen ion from NADP^{+}. NADPH oxidase catalyzes the monovalent reduction of O_2 to superoxide anion (O_2^{1}),[13] with the subsequent conversion to hydrogen peroxide (H_2O_2) by superoxide dismutase. Neutrophil-derived myeloperoxidase (MPO) converts hydrogen peroxide to hypochlorous acid ($HOCL^{-}$, bleach), which is converted to chlorine (Cl_2). The genes for the components of NADPH oxidase, their chromosomal locations, and the frequency of mutations as a cause of chronic granulomatous disease are indicated in the box. (From Leckstrom-Himes JA, Gallin JI. N Engl J Med. 2000;343:1703–14.)

cases are due to mutations affecting the X-linked gene *CYBB*, which encodes the gp91^{phox} component of the membrane cytochrome b_{558} protein complex. Rare X-linked cases have also implicated defects in glucose-6-phosphate dehydrogenase (G6PD). For this reason, most patients with CGD are boys. The other cases involve mutations of autosomal genes, including *CYBA*, which encodes p22^{phox} (the second membrane component of cytochrome b_{558}) (5% of CGD cases); *NCF-1*, which encodes p47^{phox} (20% of cases); and *NCF-2*, which encodes p67^{phox} (6% of cases) (Figure 7-2). Diagnosis is usually made by a typical clinical history and an abnormal nitroblue tetrazolium (NBT) test or another test for the neutrophil oxidative burst. Patients with CGD benefit from prophylactic treatment with trimethoprim-sulfamethoxazole and prompt antibiotic administration for specific infections. Chronic treatment with interferon-γ reduces the incidence of bacterial and fungal infections by about 70%. HSCT is curative and should be performed in patients with an HLA-matched donor in whom the clinical course or specific mutation portends a poor outcome.

Familial Mediterranean fever

Familial Mediterranean fever is characterized by sporadic paroxysmal attacks of fever, serosal inflammation, and neutrophilia. The most common presentation is recurrent attacks of acute peritonitis though pleuritis and synovitis also are frequent. It is an autosomal recessive disorder that mainly occurs in populations from the Mediterranean basin, such as Sephardic Jews, Arabs, Turks, and Armenians. However, sporadic cases have been reported in individuals of French, Italian, Greek, Belgian, and Northern European heritage. Mutations in the *MEFV* gene, which encodes a myeloid-specific protein of unclear function, appear to cause dysregulation of inflammation control that leads to unpredictable episodes of neutrophil overactivity and tissue infiltration by activated neutrophils. Because the chronic, recurrent inflammatory attacks also cause persistent elevations of serum amyloid A protein, patients with FMF are at high risk of developing complications of AA amyloidosis, especially in the kidneys. In this regard, FMF is the leading cause of secondary amyloidosis in Turkey. The diagnosis of FMF is usually made on the basis of clinical criteria, including unexplained episodes that persist over many months to years in the absence of other etiologies of inflammation. Most of the common *MEFV* mutations are well characterized. Thus, the diagnosis can now be confirmed and family studies carried out, with molecular studies done by a reference research laboratory. Colchicine prevents clinical attacks and tissue amyloid deposition in most patients with FMF. Rare patients with exceptional refractory disease have undergone successful HSCT.

FMF is the most common and prototypical disorder among the hereditary periodic fever syndromes. Hyper-IgD syndrome, which is a more rare autosomal recessive disorder found in Dutch and French families, is associated with mutations in the mevalonate kinase gene, *MVK*. The tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS, previously known as familial Hibernian fever) is an autosomal dominant disorder affecting Scottish and Irish individuals and associated with mutations in the gene encoding TNF receptor 1, *TNFRSF1A*. The autosomal dominant conditions Muckle-Wells syndrome (MWS) and familial cold urticaria (FCU, also known as familial cold autoinflammatory syndrome) are both related to mutations involving a pyrin-like protein called "NALP3," encoded by the *CIAS1* gene. Although neutrophils are not the primary mediators of pathogenesis in these non-FMF disorders, they share many clinical features with FMF and should be considered in the differential diagnosis of unexplained, recurrent fever with noninfectious autoinflammation.

Key points

- Genetic disorders affecting neutrophil function are possible, but uncommon, causes of recurrent infections, unexplained fever, and inflammation.
- Disorders affecting neutrophil adhesion, chemotaxis, and killing are usually diagnosed in young children with recurrent infections.
- Chronic granulomatous disease is characterized by recurrent bacterial and fungal infections and is due to mutations that impair the ability of phagocytes to generate reactive oxygen intermediates.
- Familial Mediterranean fever should be considered in children or adults with unexplained recurrent fever and inflammation and the appropriate ethnic background.

Monocytosis

Normally, monocytes account for approximately 1–9% of the blood leukocytes, with absolute monocyte counts ranging from 0.3–0.7 $\times$ 10^9/L. Counts above 0.8 $\times$ 10^9/L represent monocytosis. Increase in circulating monocytes is most frequently due to chronic inflammatory conditions and infectious diseases. Classic examples are tuberculosis, endocarditis, and syphilis. Monocytosis is also observed in some malignancies including lymphomas and Hodgkin disease, and inflammatory diseases of unknown cause such as sarcoidosis and SLE. Monocytosis is a hallmark of juvenile myelomonocytic leukemia, and may occur as a characteristic feature of other acute or chronic myeloproliferative/myelodysplastic conditions, such as acute monocytic leukemia and chronic myelomonocytic leukemia. In the inflammatory

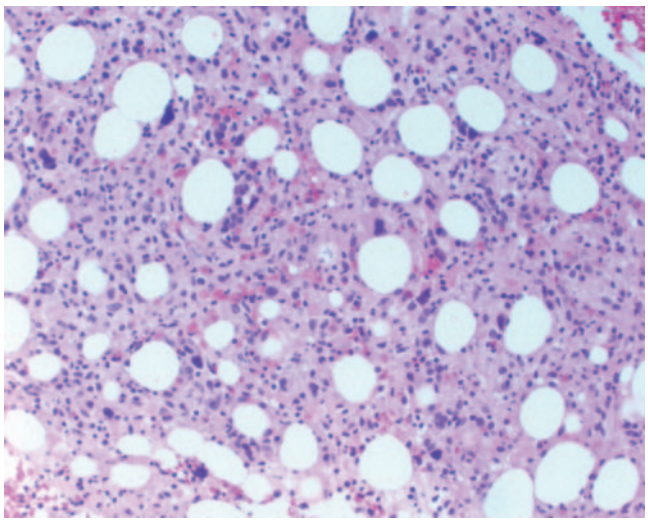
conditions associated with increased monocytes, growth factors are probably produced peripherally that stimulate monocyte production. Malignant monocytosis is presumed to be due to specific molecular defects affecting monocyte proliferation, differentiation, and survival.

A decreased absolute monocyte count can be encountered in bone marrow failure states such as aplastic anemia and less commonly myelodysplasia. Monocytopenia, along with neutropenia, is characteristic of hairy cell leukemia. Low monocyte counts are also encountered with overwhelming infections and as the result of cytotoxic chemotherapy.

Disorders of histiocytes and dendritic cells

Hemophagocytic lymphohistiocytosis

Pathologic activation and proliferation of tissue histiocytes may occur in rare patients with inherited or acquired disorders of immune regulation. These conditions are collectively referred to as hemophagocytic lymphohistiocytosis (HLH) syndromes. Children or adults with HLH present with fever, lymphadenopathy, hepatosplenomegaly, rash, neurologic signs, cytopenias, coagulopathy (especially hypofibrinogenemia), hypertriglyceridemia, and abnormal liver function tests. Tissue biopsy reveals marked infiltration by nonmalignant reactive phagocytic histiocytes along with cytotoxic $CD8^+$ T lymphocytes. These changes are most striking in the marrow, lymph nodes, spleen, and liver but can also occur in the lungs, heart, central nervous system, gastrointestinal tract, and other tissues. Pancytopenia is primarily due to the widespread consumption of blood cells in the marrow and extramedullary tissues by the cytophagocytic histiocytes (Figure 7-3). The major pathophysiologic abnormality in HLH is cytokine dysfunction, resulting in uncontrolled accumulation of activated T lymphocytes and activated macrophages in many organs. Cytokines found at high levels in the plasma of patients with HLH include interferon-γ; TNF-α;



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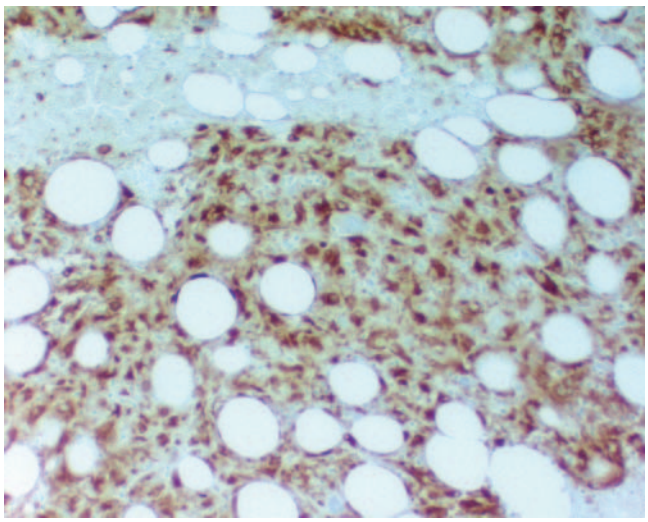

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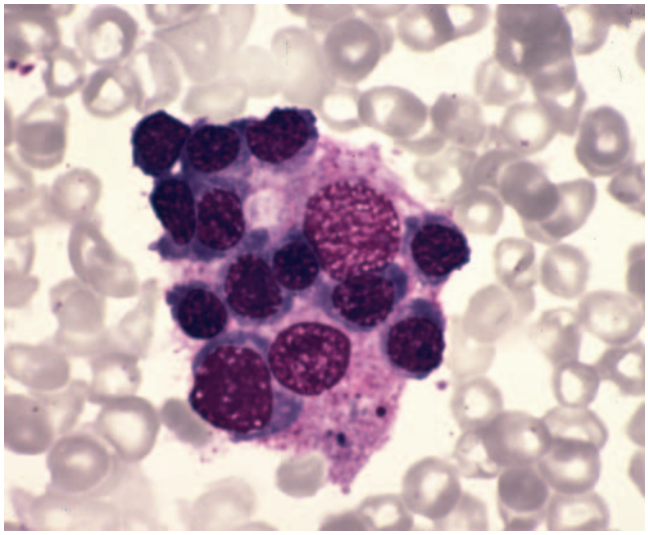


(c)

Figure 7-3 Marrow findings in hemophagocytic lymphohistiocytosis. (a) Marrow biopsy reveals increased numbers of macrophages scattered among the normal hematopoietic precursors (hematoxylin–eosin stain; original magnification 85×). (b) Immunohistochemical staining for CD68 reveals the macrophages (85×). (c) Cytophagic histiocytes are more easily identified in the marrow aspirate (Wright–Giemsa stain). (Photos courtesy of Steven J. Kussick, MD, PhD, Associate Director of Hematopathology, Assistant Professor, Department of Laboratory Medicine, University of Washington.)

interleukins (IL)-6, IL-10, and IL-12; and soluble IL-2 receptor (CD25). Elevated IL-16 levels may be important for a T_H1-type response that recruits macrophages and other cells pertinent to HLH. When disease is active, there is severely depressed NK activity and cytotoxic T-cell function.

The inherited HLH condition, which is called "familial hemophagocytic lymphohistiocytosis" (FHL), encompasses a spectrum of rare autosomal recessive diseases that present in infancy and early childhood, often in the setting of a concurrent viral infection. FHL may present as fever of unknown origin, and sporadic cases (ie, without a family history) have been mistaken for child abuse in the setting of unexplained neurologic deficits and CNS hemorrhages. A subset of children with FHL have mutations involving the *PRF1* gene, encoding perforin, which leads to defects in the ability of NK cells and cytotoxic T lymphocytes to induce apoptosis in target cells. Other mutated genes include those coding for *MUNC 13–4* and *rab27a*. These mutations lead to similar functional defects in cytotoxic T-cell and NK-cell–mediated immune regulation.

Acquired HLH syndrome, also referred to as reactive hemophagocytic syndrome or secondary HLH (SHLH), occurs in adults and children who usually have an underlying immunocompromised state and/or an infectious disease. The scope of predisposing conditions associated with SHLH is broad and includes infections, autoimmune/rheumatological disorders, hematological malignancies, (less commonly) nonhematologic malignancies, AIDS (with or without opportunistic infections), and posttransplant immunosuppression (Table 7-6). Less commonly, HLH is

Table 7-6 Conditions associated with secondary hemophagocytic lymphohistiocytosis (SHLH).

Infections

Bacterial
- *Hemophilus influenza*
- *Streptococcus pneumoniae*
- β-*Hemolytic streptococcus*
- *Streptococcus milleri*
- *Streptococcus faecalis*
- *Staphylococcus aureus*
- *Brucella abortus*
- *Salmonella typhi*
- *Escherichia coli*
- *Acinetobacter spp*
- *Mycoplasma pneumonia*
- *Chlamydia psittaci*

Viral
- Epstein–Barr virus
- Cytomegalovirus
- Varicella zoster virus
- Adenovirus
- Respiratory syncytial virus
- Parvovirus B19
- Herpes simplex virus
- Hepatitis A
- Hepatitis B
- Dengue virus

Rickettsial
- *Coxiella burnetii*
- *Ricketsia tsutsugamushi*

Fungal
- *Histoplasma capsulatum*
- *Candida albicans*
- *Cryptococcus neoformans*

Mycobacterial
- *Mycobacterium tuberculosis*

Parasitic
- *Babesia microti*
- *Leishmania donovani*

Autoimmune/rheumatologic diseases
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Sarcoidosis
- Inflammatory bowel disease
- Systemic Still disease
- Polyarteritis nodosa
- Mixed connective tissue disease
- Systemic sclerosis
- Sjogren syndrome
- Kawasaki disease
- Kikuchi disease

Neoplasms
- Acute myeloid leukemia
- Myelodysplastic syndromes
- Chronic lymphocytic leukemia
- Hodgkin lymphoma
- Non-Hodgkin lymphoma (B cell, T cell, and NK cell, including EBV-associated)
- Posttransplant lymphoma
- Myeloma
- Hairy cell leukemia
- Metastatic carcinoma
- Angiosarcoma

Immunodeficiency states
- AIDS
- Postallograft (hematopoietic stem cell or solid organ)
- Cytotoxic and/or immunosuppressive therapy
- Postsplenectomy

idiopathic. The pathophysiology of SHLH appears to be similar to that described for FLH, except that in these patients the underlying predisposing disorder, and not a congenital defect, is responsible for the secondary dysregulation of T cells and NK cells that leads to histiocyte activation.

Diagnosis and prognosis

The clinical presentation, laboratory features, and tissue histopathology of SHLH are also similar to those described for FLH. Because the familial form may not present until later in life after an inciting illness, it is neither possible nor perhaps clinically important to distinguish between the familial and the secondary forms. The HLH component of illness may not be readily apparent in a patient with underlying infection, malignancy, or active systemic autoimmune disease. HLH should be considered in the differential diagnosis of a patient who develops sepsis and/or multiple organ dysfunction syndrome (MODS) in the setting of fever, unexplained progressive pancytopenia, hypofibrinogenemia, hypertriglyceridemia, and hepatosplenomegaly. Bone marrow biopsy is crucial to identify the marked histiocytic hyperplasia and hemophagocytosis that confirm the diagnosis (Figure 7-3 and Table 7-7; cytogenetic abnormalities of chromosome 6, 9, 10, and 17 have been reported.). In addition, the marrow biopsy may be useful in cases without an apparent predisposing etiology to assess for a malignant and/or infectious cause (ie, using immunohistochemical and molecular methods). CD163, the soluble hemoglobin-haptoglobin scavenger receptor that is specific for macrophages, is also elevated in HLH and may be available through a specialty laboratory. Onset during the first few months of life and a low level of perforin expression are associated with a poor prognosis. Poor prognostic factors also include age over 30, the presence of disseminated intravascular coagulopathy, high ferritin level, high β_2-microglobulin level, recent corticosteroid treatment, severe thrombocytopenia, advanced AIDS, and high-grade lymphoma. Once the syndrome develops, median survival is only a few months without aggressive treatment. Mortality is usually due to infection and less commonly due to progressive HLH.

Table 7-7 Diagnostic criteria for hemophagocytic lymphohistiocytosis (HLC).

Major criteria[a]
1. Fever: temerature >38.5°C for > 7 days
2. Palpable splenomegaly
3. Cytopenias involving 2 or more cell lines: Hb <9.0 g/dL; platelets <100,000/μL; ANC <1000/μL
4. Hypertrigliceridemia or hypofibrinoginemia
5. Hemophagocytosis on biopsy of the bone marrow, spleen, or lymph node
Alternative criteria
1. Low or absent natural killer cell activity
2. Serum ferritin > 500 μg/L
3. Soluble CD25 > 2400 U/mL

[a]The diagnosis of HLH requires 5 major criteria. Alternative criteria (1) or (2) and (3) may substitute for a major criterion.

Adapted from Henter JI, Elinder G, Ost A. Diagnostic guidelines for hemophagocytic lymphohistiocytosis. Semin Oncol. 1991;18:29.

Treatment

Although the diagnosis of HLH requires the presence of all 5 major criteria, treatment for a presumptive diagnosis should be started if 4 of 5 criteria are fulfilled. Underlying infections or illnesses should be treated specifically. Therapy used to be a grab bag of immunosuppressive and cytotoxic therapy with very unsatisfactory results until the advent of the HLH-94 protocol. This therapy involves induction with dexamethasone and etoposide, followed by maintenance cyclosporine and intermittent pulses of dexamethasone and etoposide. A newer version, HLH-2004, is the presented recommended regimen and can be found at the Histiocytic Society Web site (www.histo.org/society). Hematopoietic stem cell transplant offers the best chance of survival to those with homozygous mutations of implicated genes, those with a family history of HLH, patients unresponsive to the first 8 weeks of therapy, and those with CNS disease. It is important the physicians using these protocols register with the Histiocytic Society so that results of treatment of this rare disease can be tracked.

Langerhans cell histiocytosis

Langerhans cell histiocytosis (LCH), a clonal disorder of Langerhans dendritic cells, is associated with polymorphic cellular infiltration and damage at either unifocal tissue sites (usually the bone; less commonly the lung, skin, or lymph nodes) or in multiple organs and tissues. Historically, localized LCH was referred to as eosinophilic granuloma, whereas clinical variants of multisystem disease were referred to as histiocytosis X, Letter–Siwe disease, and Hand–Schüller–Christian disease. LCH is rare, with an annual incidence of roughly 5 per million. An inherited risk has been implied by cases occurring in some families and identical twins. Other potential risks include a history of thyroid disease or a previous malignancy (hematologic or nonhematologic), but not a history of infection with viruses or other agents. Of note, LCH may predispose patients to subsequent malignancies. Histologically, the lesions contain a mix of characteristic Langerhans cells, which express surface CD1 a and cytoplasmic S-100, in a background of eosinophils, neutrophils, and lymphocytes (Figure 7-4). Some tumors contain an abundance of eosinophils and neutrophils with central necrosis,

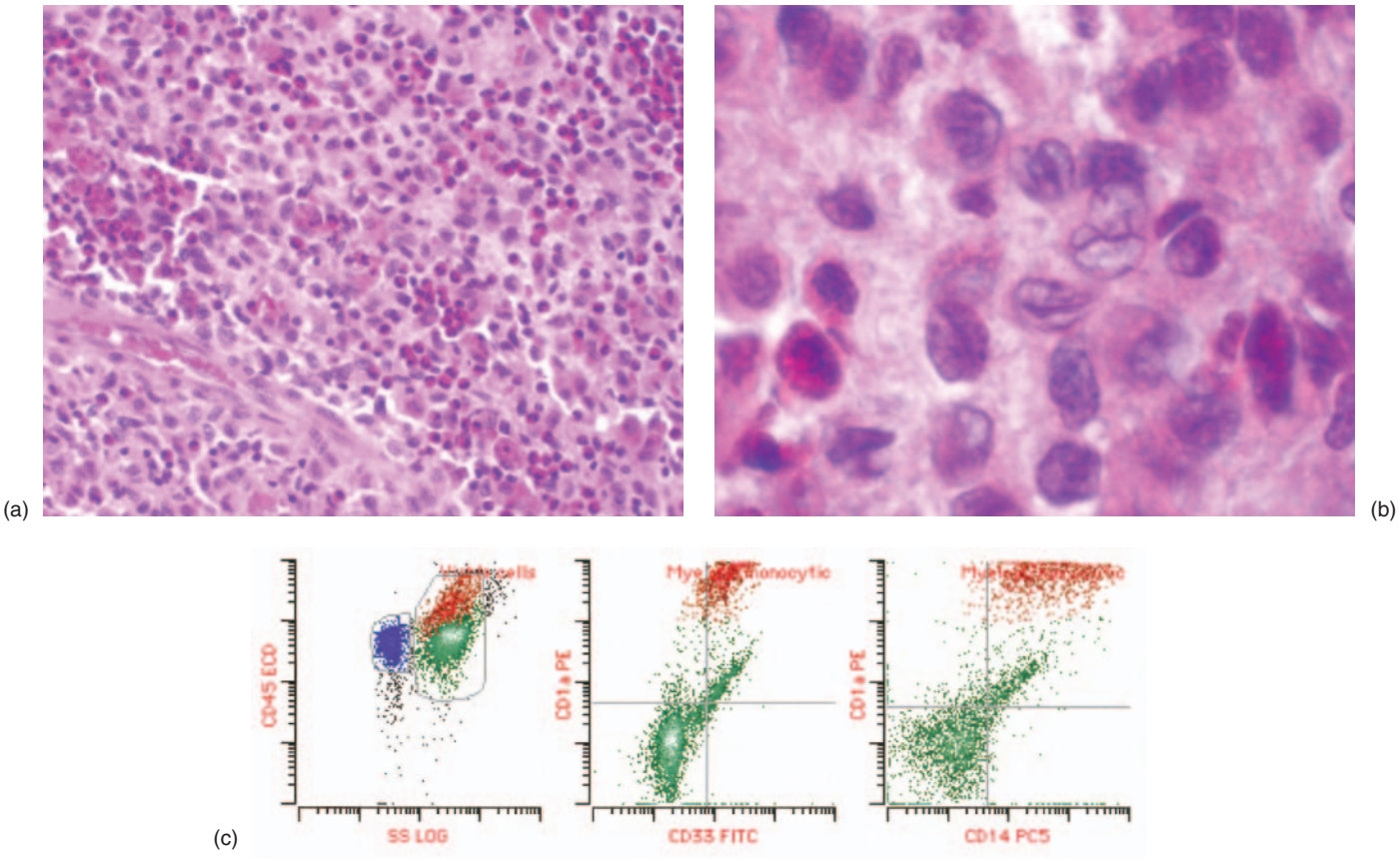


Figure 7-4 Histopathology of Langerhan cell histiocytosis (LCH). (a) LCH lesions typically consist of benign-appearing histiocytes frequently admixed with scattered eosinophils, neutrophils, and/or lymphocytes (hematoxylin–eosin stain; original magnification 85×). (b) Langerhan cells frequently have a cleaved or indented nucleus (reticulin stain; 850×). (c) Flow cytometry analysis of side scatter (SS) and CD45 expression patterns reveals lymphocytes (blue), eosinophils (green), and monocyte/macrophage cells (red) within the LCH lesion (left panel). The monocyte/macrophage cells are identified as Langerhan cells by their coexpression of CD33, CD1a, and CD14 (middle and right panels). (Photos courtesy of Steven J. Kussick, MD, PhD, Associate Director of Hematopathology, Assistant Professor, Department of Laboratory Medicine, University of Washington.)

whereas fibrosis and foamy macrophages are found in more long-standing lesions. These tumors must be differentiated from reactive processes (eg, HLH), non-Hodgkin lymphoma, and rare histiocytic and dendritic cell sarcomas (see the WHO classification reference for details). The causal genetic lesion responsible for the monoclonal outgrowth of abnormal Langerhans cells is unknown. Neither cytogenetic nor fluorescent *in situ* hybridization analyses have detected structural chromosomal abnormalities. The pathogenesis likely involves recruitment and activation of inflammatory and immune cells with local elaboration of cytokines, enzymes, and immunomodulatory factors (Figure 7-3).

LCH with either limited or multisystem involvement can occur in children or adults. Usual presentations of limited disease include persistent or recurrent/progressive bony pain and/or swelling, chronic skin rash, chronic ear drainage, dyspnea, cough, and/or pneumothorax (isolated bony involvement resulting in ear drainage is more common in children, and pulmonary disease occurs predominantly in adults). Multisystem disease may present with various combinations of bony and/or soft tissue masses, fever, eczematoid rash, gingival swelling, cough/dyspnea, tooth loss, diabetes insipidus, hepatosplenomegaly, lymphadenopathy, abnormal chest X-ray, and/or peripheral blood cytopenias. Diabetes insipidus, which is the most common CNS manifestation, occurs in up to 30% of patients and may be the initial presenting finding in LCH.

Diagnosis

Tissue biopsy is required to confirm the diagnosis of LCH. Langerhans cells are characteristically positive for CD1a, S-100, and langerin. Classic Birbeck granules can be seen by electron microscopy, although this is now rarely done for diagnosis. Erdheim–Chester disease is a systemic histiocytic disorder than can be confused with LCH, but the lesions are S-100 negative A staging workup is also required to categorize the extent and activity of disease, including older/inactive

lesions, and to guide treatment decisions. Staging studies include skeletal survey, technetium bone scan, complete chemistries, CBC, urinalysis, formal water deprivation test (if diabetes insipidus is suspected), brain MRI (to screen for occult CNS lesions), and chest X-ray. Recent studies have suggested that octreotide and PET scans may be useful in assessing disease extent and activity. Some authors[7] recommend pulmonary function tests, both as a baseline and to screen for an early obstructive defect that will require close follow-up. Additional studies should be done for suspected organ or tissue involvement (eg, hormone assays for pituitary involvement, bone marrow biopsy for cytopenias, CT scan of the abdomen for organomegaly, or abnormal liver function tests). The clinical course of limited or multisystem disease can be variable with spontaneous remissions and long symptom-free intervals occurring in some patients.

Treatment

Treatment of LCH is individualized for the extent and activity of the disease. The general management principles are similar in children and adults. Bony or soft tissue LCH limited to a single or multiple sites within the same tissue can be treated with surgical resection or bony curettage, local irradiation (usually 4–8 Gy), and/or injection of steroids. Lesions in weight-bearing bones or locations near critical structures (eg, in the inner skull) must be monitored closely. Orthopedic stabilization or more aggressive local therapy may be required in some cases. Cosmetic outcome should also be considered for skull/facial lesions. Craniofacial lesions are also at risk for developing CNS disease and may be an indication for more aggressive systemic treatment. Unfortunately, diabetes insipidus usually persists, despite hypothalamic/pituitary irradiation and successful treatment of other active sites of disease. The resulting fluid and electrolyte abnormalities are an important cause of morbidity, and even mortality, particularly in children and adolescents. Limited skin disease often responds to topical steroids, nitrogen mustard, or psoralen and UV-A (PUVA) light therapy. Management of lung disease includes discontinuation of smoking and judicious use of prednisone, vinblastine, methotrexate, and/or immunosuppressive agents. Disease-free survival with limited/local LCH is usually >95%; however, recurrences are common, and some patients require multiple courses of treatment to be cured. Patients must therefore be monitored closely for evolution to multisystem disease, secondary malignancies, and, in the case of lung involvement, progressive pulmonary compromise.

Multiagent systemic therapy is always indicated for multisystem disease commonly involving "risk organs" (spleen, liver, lung, and/or bone marrow), for single-system disease with progressive multifocal involvement (eg, multifocal bone lesions) and/or an aggressive clinical course, or for involvement of craniofacial bones. Various combinations and schedules of etoposide, vinblastine, methotrexate, prednisone, and 6-mercaptopurine have been used with additional treatments based on disease risk and initial response. High-risk patients have involvement of the lungs, marrow, liver, or spleen. Responses occur in 60–90%, with overall survival of greater than 90% in those without organ dysfunction. Lower response rates and survival of only 46–66% are seen among patients with extensive disease and organ dysfunction. Recurrences and progression are most common in patients with extensive visceral disease and suboptimal initial response to therapy. Persistent organ and endocrine dysfunction are long-term sequelae of even successful therapy. Salvage and palliative therapies include 2-chlorodeoxyadenosine, cyclosporin A, pamidronate (for bony lesions), thalidomide, interferon-γ, etanercept, liver transplantation, and HSCT. Information on available trials can be found at the Histiocytic Society Web site (www.histio.org/society).

Key points

- Reactive monocytosis can accompany certain chronic infections and malignancies, whereas chronic myelomonocytic leukemia and monocytic subtypes of acute myeloid leukemia are characterized by increased numbers of circulating malignant/atypical monocytes.
- Hemophagocytic lymphohistiocytosis (HLH) is a pathologic activation and proliferation of tissue histiocytes leading to severe multisystem clinical consequences. HLH may present in young children with an inherited predisposition (eg, due to perforin gene mutations) or in children and adults with acquired disorders of immune regulation due to infection, autoimmune disorder, malignancy, and/or acquired immunodeficiency state.
- Langerhans cell histiocytosis, a clonal dendritic cell disorder, can present in childhood or adulthood with involvement of a single tissue (usually the bone) or multiple tissues and organs including the pituitary and hypothalamus (with diabetes insipidus). The clinical course may be variable, with periods of disease inactivity and/or chronic progression, and treatment must be individualized.

Mastocytosis

Mastocytosis refers to a spectrum of entities characterized by inappropriate tissue accumulation of atypical or, less commonly, frankly malignant mast cells (Table 7-8). Cutaneous mastocytosis (CM), which is confined to the skin, accounts for roughly 80% of all cases and is the most common mast cell disorder affecting children. CM typically presents as a maculopapular eruption (also called "urticaria pigmentosa")

Table 7-8 WHO classification of mastocytosis.

Cutaneous mastocytosis
Urticaria pigmentosa/maculopapular cutaneous mastocytosis
Diffuse cutaneous mastocytosis
Solitary mastocytoma of skin
Indolent systemic mastocytosis
Bone marrow mastocytosis
Smoldering systemic mastocytosis
Aggressive systemic mastocytosis
Systemic mastocytosis with associated clonal hematological nonmast cell lineage disease
Mast cell leukemia
Mast cell sarcoma
Extracutaneous mastocytoma

Adapted from Valent P, Horny HP, Li CY, et al. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. In: Jaffe ES, Harris NL, Stein H, et al., eds. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2001.

and less commonly as diffuse erythema, plaques, nodules, or isolated tumors (ie, mastocytomas). By comparison, systemic mastocytosis (SM) involves the skin and/or extracutaneous tissues and occurs predominantly in adults. SM accounts for 15–20% of mastocytosis cases and, in a majority of patients, is associated with mutations involving *KIT*, the gene encoding the c-Kit tyrosine kinase receptor. The characteristic mutation, an Asp-816-Val substitution, constitutively activates the receptor and therefore likely plays an important pathogenetic role. Notably, the Asp-816-Val mutation has been found in the hematopoietic progenitors of some patients with SM, indicating that mastocytosis may reflect a myeloproliferative disorder in some cases. By contrast, clonal mutations of *c-Kit* are not found with CM. However, increased local concentrations of SCF, the c-Kit ligand, are found in CM lesions.

Diagnosis of CM and SM

Diagnostic criteria for CM, SM, and the indolent and aggressive forms of SM have been established by the WHO (Table 7-9). Those disorders are differentiated from mast cell leukemia, mast cell sarcoma, and cases of SM associated with underlying clonal nonmast cell hematological malignancies. The differential diagnosis of CM and SM also includes benign skin disorders, cutaneous flushing, angioneurotic edema, pheochromocytoma, hyper-IgE syndrome, complement disorders, Zollinger–Ellison syndrome, carcinoid syndrome, idiopathic anaphylaxis, reactive mast cell hyperplasia (due to infections, malignancies, or other underlying disease), and atypical myeloid leukemias.

The tissue mast cells in CM and SM lesions share phenotypic and functional features with their normal counterparts. They produce and secrete a wide variety of vasoactive mediators, cytokines, and enzymes, including histamine, heparin, prostaglandins, TNF, transforming growth factor-β (TGF-β), IL-5, IL-6, chemokines, tryptase, and proteases. These mast cell products, in addition to the infiltrative nature of the cells, play important roles in disease pathogenesis, clinical signs, and symptoms. Presenting complaints with SM can include headache, malaise, severe fatigue, cachexia, flushing, pruritus/urticaria, bronchospasm, abdominal cramping, diarrhea, epigastric pain/dyspepsia, and bone pain. Symptoms may be exacerbated by temperature change and alcohol. Physical findings may include dermatographism (Darier sign), lymphadenopathy, hepatosplenomegaly, ascites, bone swelling, or pathologic fractures.

The diagnosis of CM is confirmed by a skin biopsy that identifies infiltrates of mast cells (ie, by characteristic immunophenotype, tryptase/chymase staining, or both) without evidence for systemic disease. Serum tryptase level is normal with CM. SM is usually diagnosed by identifying aggregates of atypical mast cells in a biopsy of the marrow, the most commonly affected tissue (Figure 7-5). The diagnosis of SM can also be made by demonstrating involvement of an extracutaneous tissue, by identifying the *KIT* mutation at position 816, and by finding an elevated level of total serum tryptase (Table 7-9). Measurement of 24-hour urine histamine may also helpful in the diagnosis of SM as some patients are α-tryptase deficient, making total serum tryptase an unreliable marker.

Treatment of CM and SM

Treatment of CM includes H_1 and H_2 antihistamines, cromolyn, topical or intralesional glucocorticoids, and PUVA therapy. The prognosis is good, and most children with CM will outgrow their disease. Adults with chronic CM may require long-term continuous or intermittent symptomatic treatment. Adults with CM rarely evolve to SM. Most adults with SM have the indolent variant, which follows a relatively benign course. Treatment is usually symptomatic, with antihistamines, anticholinergics, proton pump inhibitors, cromolyn, and/or PUVA. Aspirin or nonsteroidal anti-inflammatory drugs have been helpful for some patients with flushing and syncope (hypersensitivity to the drugs must be excluded). Patients with organomegaly and/or more marked marrow involvement (provisionally referred to as "smoldering SM") should be monitored for evolution to aggressive SM. Symptomatic SM in the presence of a nonmast cell clonal hematologic disease should be treated as indicated both for the hematologic malignancy and for the SM complications.

Table 7-9 WHO criteria for cutaneous and systemic mastocytosis.

Cutaneous mastocytosis
Typical skin lesions demonstrating the typical clinical findings and typical infiltrates of mast cells in a multifocal or diffuse pattern in an adequate skin biopsy

Systemic mastocytosis
Major criteria
Multifocal, dense infiltrates of mast cells (15 or more mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s), and confirmed by tryptase immunohistochemistry or other special stains

Minor criteria
a. In biopsy sections of bone marrow or other extracutaneous organs, more than 25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology, or, of all mast cells in bone marrow aspirate smears, more than 25% are immature or atypical mast cells
b. Detection of *KIT* point mutation at codon 816 in bone marrow, blood, or other extracutaneous organ(s)
c. Mast cells in bone marrow, blood, or other extracutaneous organs that coexpress CD117 with CD2 and/or CD25
d. Serum total tryptase persistently $>$ 20 ng/mL (unless there is an associated clonal myeloid disorder, in which case this parameter is not valid)
The diagnosis of SM may be made if 1 major and 1 minor criterion are present, or, if 3 minor criteria are fulfilled

Systemic mastocytosis with associated clonal hematological nonmast cell lineage disease
Meets criteria for SM *and*
Associated clonal hematological nonmast cell lineage disorder (MDS, MPD, AML, lymphoma, or other hematological neoplasm that meets the criteria for a distinct entity in the WHO classificiation)

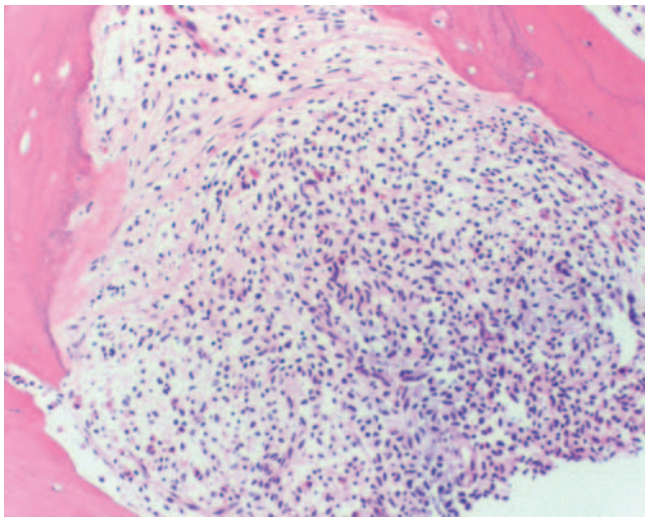
Indolent systemic mastocytosis
Meets criteria for SM
No evidence of an associated clonal hematological malignancy/disorder
No "B" or "C" findings
Mast cell burden is low and skin lesions are almost invariably present
Bone marrow mastocytosis (provisional subvariant): bone marrow involvement, but no skin lesions
Smoldering systemic mastocytosis (provisional subvariant): with 2 or more "B" findings but no "C" findings

Aggressive systemic mastocytosis
Meets criteria for SM
One or more "C" findings
No evidence of an associated clonal hematological malignancy/disorder
No evidence of mast cell leukemia
Lymphadenopathic mastocytosis with eosinophilia (provisional subvariant): progressive lymphadenopathy with peripheral blood eosinophilia, often with extensive bony involvement, and hepatosplenomegaly, but usually without skin lesions

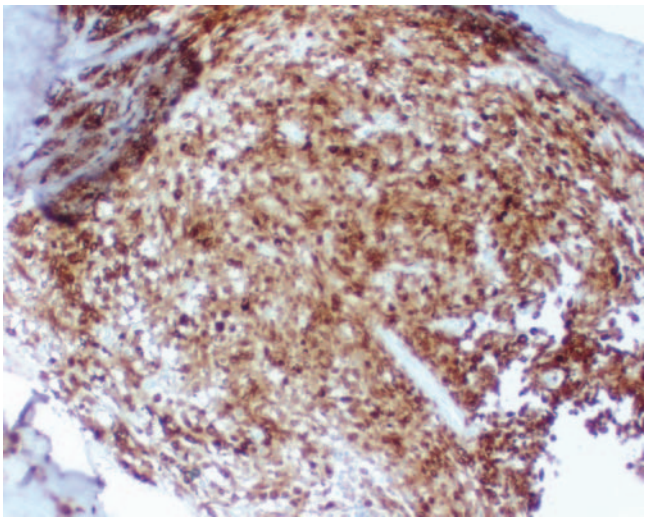
"B" Findings
1. Bone marrow biopsy showing $>$ 30% infiltration by mast cells (focal, dense aggregates) and/or serum total tryptase level $>$ 200 ng/mL
2. Signs of dysplasia or myeloproliferation, in nonmast cell lineage, but insufficient criteria for definitive diagnosis of hematopoietic neoplasm by WHO, with normal or only slightly abnormal blood counts
3. Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or palpable or visceral lymphadenopathy

"C" Findings
1. Bone marrow dysfunction manifested by one or more cytopenia (ANC $< 1 \times 10^9$/L, Hgb $<$ 10 g/dL, or platelets $< 100 \times 10^9$/L), but no frank nonmast cell hematopoietic malignancy
2. Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension
3. Skeletal involvement with large-sized osteolysis and/or pathological fractures
4. Palpable splenomegaly with hypersplenism
5. Malabsorption with weight loss due to GI mast cell infiltrates

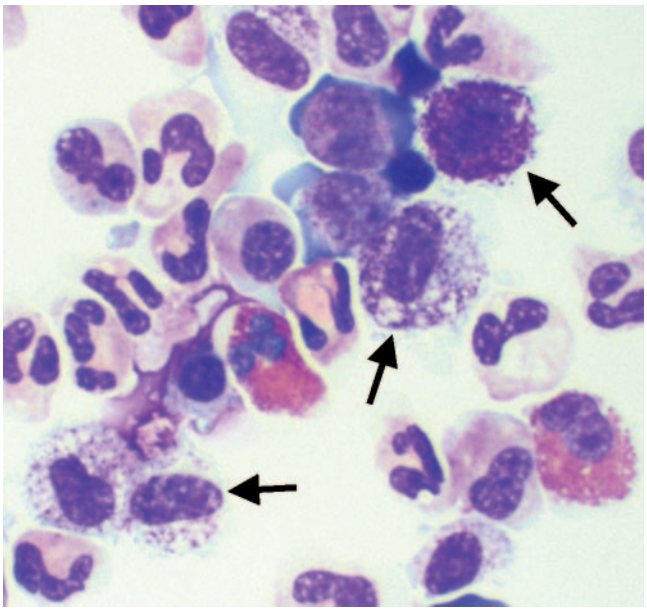
Adapted from Valent P, Horny H-P, Li CY, et al. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. In: Jaffe ES, Harris NL, Stein H, et al., eds. World Heath Organization Classification of Tumours. Lyon: IARC Press; 2001.



(a)



(b)



(c)

Figure 7-5 Marrow involvement with systemic mastocytosis. (a) Marrow biopsy may show areas of scattered infiltration or complete replacement by elongated, spindle-shaped cells (hematoxylin–eosin stain; original magnification 85×). (b) Tryptase staining of the biopsy identifies the infiltrating cells as mast cells. (c) Abnormal mast cells may also be identified in marrow aspirate specimens; however, this is not a reliable assay for the diagnosis (Wright–Giemsa stain; 425×). (Photos courtesy of Steven J. Kussick, MD, PhD, Associate Director of Hematopathology, Assistant Professor, Department of Laboratory Medicine, University of Washington.)

The aggressive variant of SM may progress to end-stage organ fibrosis and/or failure, pathologic fractures, and/or severe cytopenias. Transformation to mast cell leukemia can also occur over a short or prolonged period of follow-up. Treatment of aggressive SM should be individualized. Interferon-α alone can be helpful for patients with painful skeletal lesions or those that threaten structural integrity. Corticosteroids are avoided because of their adverse effects on bone. Patients with hepatosplenomegaly, ascites, portal hypertension, malabsorption, and/or marrow suppression without major bony complications should receive a combination of corticosteroids and interferon-α. Roughly half of patients will respond to this regimen, although most are partial responses. Occasional nonresponders may benefit from 2-chlorodeoxyadenosine. Of note, a recent pilot study reported that single-agent 2-chlorodeoxyadenosine, given as 5-day treatment cycles every 4 to 6 weeks, induced clinical and laboratory responses (ie, decreased serum tryptase and urinary histamine metabolites) in 10 of 10 patients with symptomatic SM (including 4 with indolent/smoldering SM, 3 with aggressive SM, and 3 with SM and accompanying hematologic malignancy). Additional data are needed to confirm the efficacy and safety of this agent and to determine its role in the overall treatment approach in symptomatic patients. Patients who fail to respond or progress to mast cell leukemia should receive multiagent antileukemic chemotherapy. HSCT should be considered for those patients who achieve a remission.

The crucial role of c-Kit in normal mast cell development, and the recent evidence that *KIT* mutations may be important in disease pathogenesis, prompted studies to treat mastocytosis patients with the nonselective c-Kit tyrosine kinase inhibitor imatinib mesylate. No clinical responses were seen among cases with the Asp-816-Val mutation, and it was subsequently appreciated that the mutation, which affects the

catalytic pocket of the protein, prevents imatinib binding and inhibitory activity. However, a subset of patients with SM and eosinophilia were found to respond to imatinib, and none of these patients had the Asp-816-Val mutation. Further studies of those cases revealed a different genetic rearrangement involving an interstitial deletion on the long arm of chromosome 4 that brings the gene encoding platelet-derived growth factor receptor *a* (*PDGFA*) into juxtaposition with the Fip1-like 1 gene (*FIP1L1*). The *FIP1L1-PDGFA* fusion gene, previously identified in roughly half of patients with hypereosinophilic syndrome (HES, see Chapter 8), gives rise to a chimeric PDGFα protein with constitutive tyrosine kinase activity. Imatinib effectively inhibits this activity and induces clinical responses in those patients with HES or the eosinophilia variant of SM associated with the *FIP1L1-PDGFA* rearrangement.

Key points

- Mastocytosis is characterized by tissue infiltration of atypical dysregulated mast cells. Mast cell infiltration may be confined to the skin (ie, cutaneous mastocytosis) or involve extracutaneous tissues (ie, systemic mastocytosis).
- The clinical manifestations of cutaneous and indolent systemic mastocytosis are primarily caused by mast cell–derived vasoactive mediators, cytokines, enzymes, and other bioactive factors. Treatment in those cases is primarily symptomatic and supportive.
- Aggressive systemic mastocytosis can lead to severe bony and/or end-organ complications or to mast cell leukemia. Systemic treatment with interferon-α, with or without corticosteroids, or chemotherapeutic agents is required.
- Some cases of mastocytosis associated with eosinophilia and mutations in the PDGFRα kinase receptor respond to treatment with imatinib mesylate.

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Hemphagocytic lymphohistiocytosis (HLH)

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This report details the outcome of children with mostly the familial form of HLH from data collected by the Histiocytic Society through its International Registry for HLH. These data suggest that hematopoietic stem cell transplant offers the best chance for survival in children with familial HLH.

Chen TL, Wong WW, Chiou TJ. Hemophagocytic syndrome: an unusual manifestation of acute human immunodeficiency virus infection. Int J Hematol. 2003;78:450–2.

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Janka GE, Schneider EM. Modern management of children with hemophagocytic lymphohistiocytosis. Br J Hematol. 2004;124:4–14.

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Neeft M, Wieffer M, de Jong AS, et al. Munc13–4 is an effector of rab27 a and controls secretion of lysosomes in hematopoietic cells. Mol Biol Cell. 2005;16:731–41. Epub 2004 Nov 17.

This report details how Munc13–4 and rab27a interact with one another in normal cytolytic granules fusion, and how mutation in either can be associated with HLH.

Stepp SE, Dufourcq-Lagelouse R, Le Deist F, et al. Perforin gene defects in familial hemophagocytic lymphohistiocytosis. Science. 1999;286:1957–9.

Linkage analyses indicated that FHL is genetically heterogeneous and linked to 9q21.3–22, 10q21–22, or another as yet undefined locus. Sequencing of the coding regions of the perforin gene of 8 unrelated 10q21–22-linked FHL patients revealed homozygous nonsense mutations in 4 patients and missense mutations in the other 4 patients. Cultured lymphocytes from patients had defective cytotoxic activity, and immunostaining revealed little or no perforin in the granules. Thus, defects in perforin were responsible for 10 q21–22-linked FHL.

Schaer DJ, Schleiffenbaum B, Kurrer M, et al. Soluble hemoglobin-haptoglobin scavenger receptor CD163 as a lineage-specific marker in the reactive hemophagocytic syndrome. Eur J Hematol. 2005;74:6–10.

These data suggest CD163 is a macrophage-specific marker in patients with disorders of inappropriate macrophage activation.

Langerhans cell histiocytosis (LCH)

Braier J, Latella A, Balancini B, et al. Outcome in children with pulmonary Langerhans cell histiocytosis. Pediatr Blood Cancer. 2004;43:765–9.

This retrospective evaluation of LCH patients was performed from 1987 to 2001. All had skin, bone, or lymph node involvement. Chest X-ray was performed in all patients and computed tomography (CT) in 21. Median follow-up of all multisystem patients was 2.1 years, with a 5-year survival probability of .59. Pulmonary compromise without other risk organ involvement did not appear to be a negative prognostic factor.

Calming U, Bemstrand C, Mosskin M, et al. Brain 18-FDG PET scan in central nervous system Langerhans cell histiocytosis. J Pediatr. 2002;141:435–40.

Functional scanning with FDG-PET may be able to discern disease activity.

Calming U, Jacobsson H, Henter JI. Detection of Langerhans cell histiocytosis lesions with somatostatin analogue scintigraphy–a preliminary report. Med Pediatr Oncol. 2000;35:462–7.

Preliminary report on the utility of octreotide scanning in the staging of LCH.

Grois N, Potschger U, Prosch H, et al. Risk factors for diabetes insipidus in Langerhans cell histiocytosis. Pediatr Blood Cancer. 2005 Jul 26.

This report details the outcome of 1741 patients with LCH registered on the trials DALHX 83, DALHX 90, LCH I, and LCH II were studied. Patients with multisystem disease and craniofacial involvement at diagnosis, in particular of the ear, the eye, and the oral region, carry a significantly increased risk to develop diabetes insipidus during their course. This risk is augmented when the disease remains active for a longer period or reactivates.

Howarth DM, Gilchrist GS, Mullan BP, et al. Langerhans cell histiocytosis: diagnosis, natural history, management, and outcome. Cancer. 1999;85:2278–90.

This was a descriptive analysis of 314 patients with LCH followed at the Mayo. Conclusions included that patients with isolated bone LCH lesions have the best prognosis compared with patients with LCH involvement of other systems. By contrast, 20% of patients with multisystem involvement have a progressive disease course despite treatment.

Veyssier-Belot C, Cacoub P, Caparros-Lefebvre D, et al. Erdheim-Chester disease. Clinical and radiologic characteristics of 59 cases. Medicine (Baltimore). 1996;75:157–69.

Erdheim–Chester disease (ECD) may be confused with Langerhans cell histiocytosis as it sometimes shares the same clinical (exophthalmos, diabetes insipidus) or radiologic (osteolytic lesions) findings. This report details the distinctive features of ECD: patients are older and have a worse prognosis than those with Langerhans cell histiocytosis, and the diagnosis relies on the association of specific radiologic and histologic findings.

Weitzman S, Wayne AS, Arceci R, et al. Nucleoside analogues in the therapy for Langerhans cell histiocytosis: a survey of members of the histiocyte society and review of the literature. Med Pediatr Oncol. 1999;33:476–81.

Report on the results of a survey to members of the Histiocytic Society on treatment results of 15 patients treated with the purine analogues 2-CdA and 2′-DCF. These agents appear to have a useful role in LCH and are worthy of prospective trial in patients unresponsive to routine therapy.

Willis B, Ablin A, Weinberg V, et al. Disease course and late sequelae of Langerhans' cell histiocytosis: 25-year experience at the University of California, San Francisco. J Clin Oncol. 1996;14:2073–82.

A retrospective review of 71 patients with LCH followed at UCSF. Despite the favorable survival, more than half of LCH patients will have further dissemination of disease or late sequelae, including even some patients with single-system disease at diagnosis. The authors concluded that long-term treatment should be explored to determine if this might ameliorate long term complications.

Willman CL, Busque L, Griffith BB, et al. Langerhans'-cell histiocytosis (histiocytosis X)–a clonal proliferative disease. N Engl J Med. 1994;331:154–60.

The detection of clonal histiocytes in all forms of Langerhans cell histiocytosis indicates that this disease is probably a clonal neoplastic disorder with highly variable biologic behavior.

Mastocytosis

Furitsu T, Tsujimura T, Tono T, et al. Identification of mutations in the coding sequence of the proto-oncogene c-kit in a human mast cell leukemia cell line causing ligand-independent activation of c-kit product. J Clin Invest. 1993;92:1736–44.

The results of this study showed that conversion of Asp-816 to Val in human c-kitR was an activating mutation and responsible for the constitutive activation of c-kitR in HMC-1 cells.

Longley BJ Jr, Morganroth GS, Tyrrell L, et al. Altered metabolism of mast-cell growth factor (c-kit ligand) in cutaneous mastocytosis. N Engl J Med. 1993;328:1302–7.

This study documented the increased local concentrations of soluble c-kit ligand (stem cell factor) in the skin of patients with cutaneous mastocytosis.

Pardanani A, Elliott M, Reeder T, et al. Imatinib for systemic mast-cell disease. Lancet. 2003;362:535–6.

The investigators prospectively treated 12 adults with symptomatic systemic mast cell disease with imatinib at a dose of either 100 mg or 400 mg per day. Of the 10 patients who could be assessed for response, 5 (50%) had a measurable response to the drug, 4 of whom had important mast cell cytoreduction and 2 of whom had complete clinical and histologic remission. In the 5 patients with eosinophilia, 3 had complete clinical and hematological remission. The other 2, who did not respond to treatment, were the only patients with the c-kit D816V mutation.

Parker RI. Hematologic aspects of systemic mastocytosis. Hematol Oncol Clin North Am. 2000;14:557–68.

Schwartz LB, Irani AM. Serum tryptase and the laboratory diagnosis of systemic mastocytosis. Hematol Oncol Clin North Am. 2000;14:641–57.

Total tryptase levels of 20 ng/mL or higher in a baseline serum sample when the ratio of total to β-tryptase is 20 or greater strongly suggest underlying systemic mastocytosis. Although the absolute level of total tryptase does not predict disease severity, it may provide a

practical method for assessing the efficacy of therapeutic interventions designed to reduce the mast cell burden.

Valent P, Akin C, Sperr WR, et al. Diagnosis and treatment of systemic mastocytosis: state of the art. Br J Hematol. 2003;122:695–717.

Comprehensive review of the diagnosis and treatment of SM.

Valent P, Sperr WR, Schwartz LB, et al. Diagnosis and classification of mast cell proliferative disorders: delineation from immunologic diseases and nonmast cell hematopoietic neoplasms. J Allergy Clin Immunol. 2004;114:3–11; quiz 12.

This review provides an overview of mastocytosis and its subvariants and a practical guide that might help to delineate mastocytosis from unrelated systemic disorders.

Worobec AS. Treatment of systemic mast cell disorders. Hematol Oncol Clin North Am. 2000;14:659–87, vii.

The heterogeneous nature of disease manifestations in mastocytosis requires the individualization of therapy to each patient's clinical presentation and prognosis. The mainstay of treatment of most categories of mastocytosis is H_1 and H_2 antihistamines with the addition of corticosteroids for more severe symptoms. This article presents a summary of treatment strategies for indolent and aggressive forms of mastocytosis along with a discussion of future therapeutic directions.

Worobec AS, Semere T, Nagata H, et al. Clinical correlates of the presence of the Asp816Val c-kit mutation in the peripheral blood mononuclear cells of patients with mastocytosis. Cancer. 1998;83:2120–9.

The overall prevalence of the Asp-816-Val mutation in the catalytic domain of the c-kit receptor in this series of 65 patients was 25%. The presence of the Asp-816-Val mutation in PBMCs was observed in 15 adults and 1 infant, but not in any children with mastocytosis. Patients whose PBMCs were positive for this mutation manifested a more severe disease. These patients more commonly had osteosclerotic bone involvement (a clinical feature primarily observed in mastocytosis patients with an associated hematologic disorder) as well as immunoglobulin dysregulation and peripheral blood abnormalities.