Why Does My Patient Have Leukocytosis?

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Leukocytosis is an increase of the white blood cell (WBC, or leukocyte) count; for adults, this is usually more than 11,000/μL. The term leukocyte refers collectively to granulocytes (neutrophils, eosinophils, and basophils), monocytes, and lymphocytes. Any of these individual lineages, or combinations of them, may account for increased WBC.

Leukocytosis is one of the most commonly encountered laboratory abnormalities in clinical medicine, and is a frequent reason for both outpatient and inpatient consultation by a hematologist. Leukocytosis may be an acute or chronic process. It is most often caused by an appropriate physiologic response of normal bone marrow to an infectious or inflammatory stimulus. Less frequently, leukocytosis is caused by a primary bone marrow disorder, such as leukemia, lymphoma, or a myeloproliferative neoplasm. Defining the cause of leukocytosis demands a thorough clinical history, physical examination, and review of the peripheral blood smear, and may require additional laboratory testing, radiologic imaging, bone marrow examination, and molecular or cytogenetic analyses.

WHITE BLOOD CELL (WBC) DEVELOPMENT

Three-quarters of all nucleated cells in the bone marrow are committed to the production of leukocytes. Each day, approximately 1.6 billion leukocytes are produced per kilogram of body weight, and more than half are neutrophils.[1]

The peripheral WBC count is an indirect measure of the body's total mass of leukocytes, because only 2% to 3% of total leukocytes circulate in the bloodstream; 90% of

WBCs are present in bone marrow stores and 7% to 8% are stored in other tissues.[1] The WBC count, as measured in a peripheral blood complete blood count (CBC), is influenced by changes in: (1) the size of the bone marrow storage pool; (2) the rate of WBC release from storage pools; (3) the balance of actively circulating WBC versus reversibly adherent (marginated) cells; and (4) rates of migration to, and consumption of, leukocytes in peripheral tissues.

DEVELOPMENT, MATURATION, AND SURVIVAL OF GRANULOCYTES

Despite their distinctive appearances, functions, and patterns of gene/protein expression, all cellular elements of peripheral blood, that is, red blood cells (RBCs), platelets, and WBCs, ultimately arise from hematopoietic stem cells (HSCs). This rare population of bone marrow cells (<0.2%) has the ability to both self-renew and give rise to more differentiated committed progenitor cells, which are committed to specific cellular lineages, including precursors to granulocytes, monocytes, lymphocytes, RBCs, and megakaryocytes. HSCs and progenitor cells are mononuclear cells morphologically indistinguishable from lymphocytes, but they can be identified in the bone marrow by their expression of antigens such as CD34.[1]

Differentiating granulocytes pass through 6 successive, morphologically distinct stages of maturation. The earliest recognizable form is the myeloblast, followed in turn by promyelocytes and myelocytes; together, these cells constitute the proliferative pool of myeloid cells. The later stages of neutrophil maturation, that is, metamyelocytes, bands and, ultimately, polymorphonuclear neutrophils (polys), are postmitotic.[1] Maturation of granulocytes is marked by nuclear condensation and eventual segmentation (hence the term polymorphonuclear), and acquisition of cytoplasmic granules, which contain pools of degradative enzymes and other products required for effective bacterial killing.

The bone marrow reserve of maturing neutrophils represents approximately a 1-week supply. This storage pool allows a rapid response to demand for WBCs and can triple the level of circulating leukocytes within hours. Neutrophils that leave the marrow can circulate, marginate, or enter peripheral tissues. Margination is the process whereby neutrophils reversibly adhere to the blood vessel wall using specialized adhesion molecules. When stimulated by infection, inflammation, drugs, or metabolic toxins, these cells can demarginate to enter the pool of freely circulating leukocytes. Granulocytes remain in circulation or in peripheral tissues for only a few hours before cell death. The estimated total life span of maturing granulocytes is 11 to 16 days, most of which involves bone marrow maturation and storage.[1]

Based on the staining qualities of their cytoplasmic granules, 3 major granulocytic subgroups are recognized. Most granulocytes are neutrophils (50%–70% of circulating leukocytes), whereas eosinophils and basophils typically constitute only 1% to 2% each. The specialized contents of their distinctive granules support their important roles in bacterial killing (neutrophils), parasitic infections (eosinophils), and viral infections or allergic immune reactions (basophils).

DEVELOPMENT OF MONOCYTES

Monocytes develop from a granulocyte-monocyte precursor that also gives rise to the granulocyte lineage. Under the influence of specialized cytokines, monocytes transform into macrophages that reside in peripheral tissues. Monocytes are the largest mature cells in circulation, and play major roles in phagocytosis and regulation of the immune response.[1]

LYMPHOCYTE DEVELOPMENT

There are 2 major categories of lymphocytes, B cells and T cells, and lesser lymphocyte populations, including natural killer (NK) cells. B lymphocytes are responsible for generating the enormous range of highly specific antibodies (immunoglobulins) that are required for effective immune function. B cells arise in the bone marrow, rearrange their immunoglobulin genes in lymph nodes after antigen exposure, and take up residence in lymph nodes. A subset of B lymphocytes further matures into plasma cells, which primarily reside in bone marrow and generate large quantities of immunoglobulins in response to infectious or inflammatory challenges.

T lymphocytes originate in the bone marrow, mature in the thymus, and take up residence in lymph nodes, bone marrow, and peripheral tissues. Cytotoxic T cells can directly attack abnormal or infected cells (ie, bearing viral antigens on their cell surface), and modulate the activity of B cells and other aspects of the immune system. T-helper cells secrete cytokines that augment specific immune responses. By contrast, T-suppressor or regulatory cells secrete cytokines that can dampen the intensity of immune response after the infectious agent is cleared. NK cells, a subpopulation of lymphocytes, lack most of the recognizable surface markers of mature T or B cells. NK cells can nonspecifically target cancer cells or microorganisms. The term large granular lymphocytes (LGLs) usually refers to NK cells, because up to 75% of LGLs function as NK cells.[1]

EVALUATION OF LEUKOCYTOSIS

The clinical evaluation of leukocytosis is influenced by (1) the nature of the cells involved, (2) the duration of the leukocytosis, and (3) the presence of associated clinical findings. The differential count from a CBC and review of the peripheral blood smear will define whether the increased leukocytes are predominantly granulocytes or lymphocytes, detect abnormalities of WBC morphology, and identify abnormalities of other lineages (eg, anemia, polycythemia, or platelet abnormalities).

The duration of leukocytosis, that is, hours to days versus weeks, months, or years, influences the likely underlying cause. A short duration of leukocytosis suggests an acute event, such an infection or acute leukemia. By contrast, long-standing leukocytosis may represent chronic inflammatory states or hematologic malignancies, such as chronic leukemias or lymphomas. Similarly, the presence of associated clinical findings may point to an underlying systemic illness or reflect consequences of a primary hematologic disorder.

CLASSIFICATION OF LEUKOCYTOSIS

The following terms refer to the level and nature of leukocytosis, but do not have strict definitions and may be applied loosely by clinicians. Left shift refers to an increased percentage of immature granulocyte forms in the peripheral blood, which may exhibit toxic granulations (prominent primary granules) and Döhle bodies (prominent secondary granules) in response to severe infections. The presence of myelocytes or even less mature granulocyte forms in peripheral blood should raise the question of an underlying hematologic malignancy or severe trauma.

Leukemoid reactions represent exaggerated leukocytosis (typically 50,000–100,000/μL) and may include in the peripheral blood all recognizable stages of neutrophil maturation, that is, from myeloblasts to mature granulocytes. Leukemoid reactions typically last hours to days and may be caused by either benign or malignant conditions. A leukoerythroblastic reaction caused by myelophthisis is similar (but the

total WBC does not need to be high) and also includes nucleated RBCs. Leukoery-throblastosis indicates severe disruption of the marrow by overwhelming infection, myelofibrosis, or bone marrow invasion by cancer, and may be associated with extra-medullary hematopoiesis. A leukoerythroblastic reaction in infants can occur with severe hemolytic anemia (eg, erythroblastosis fetalis) or the rare bone disorder, osteo-petrosis, in which failure of osteoclasts to resorb bone causes loss of hematopoietic marrow space and resultant extramedullary hematopoiesis.

Hyperleukocytosis refers to a WBC count greater than 100,000/μL, and is seen almost exclusively in leukemias and myeloproliferative disorders. Leukostasis, or sludging of WBC in small vessels of the brain, lungs, and kidneys, is an oncologic emergency that may cause life-threatening cerebral infarcts, cerebral hemorrhage, or pulmonary insufficiency caused by impaired blood flow. Leukostasis is more common in acute myelogenous leukemia than in acute lymphoblastic leukemia, because myeloblasts are larger and more adhesive than lymphoblasts; it is rarely seen in chronic leukemias, even with extremely high WBC counts.[2,3]

DISTINGUISHING A PRIMARY HEMATOLOGIC DISORDER FROM A REACTIVE (SECONDARY) LEUKOCYTOSIS

When evaluating leukocytosis, attempts should be made to distinguish a primary hematologic disorder (such as leukemias and myeloproliferative neoplasms) from a secondary effect, that is, the response of normal bone marrow to an infectious or inflam-matory challenge. A careful history and physical examination, review of the peripheral blood smear, and laboratory studies are important for making this distinction. Ultimately bone marrow examination, including morphology, chromosome analysis, molecular testing, and imaging studies may be required to conclusively distinguish between these categories of leukocytosis.

True Leukocytosis Versus Pseudoleukocytosis

Leukocytosis may result from (1) increased production, (2) mobilization of storage pools, (3) reduced adhesion to vascular endothelium, (4) decreased migration to periph-eral tissues, (5) increased cell survival, or (6) combinations of these processes. Pseudo-neutrophilia may result from granulocyte demargination due to exercise, epinephrine, or anesthesia. Because the normal spleen retains a large number of leukocytes, asplenia is associated with an increased WBC count. Corticosteroids, which demarginate granu-locytes, decrease neutrophil release from the marrow, and reduce neutrophil egress from the circulation, frequently cause leukocytosis.

CAUSES OF SECONDARY LEUKOCYTOSIS
Infections

Bacterial infections typically cause mild to moderate leukocytosis (11,000–30,000/μL), with a preponderance of mature neutrophils and bands (**Box 1**). The granulocytosis is usually of short duration, and may be associated with a left shift and toxic granulations or Döhle bodies. WBC counts may transiently decline early in the course of over-whelming sepsis, only to increase later. Some patients with *Clostridium difficile* infec-tion or tuberculosis may manifest a leukemoid reaction with a WBC count greater than 50,000/μL. Conversely, typhoid fever, brucellosis, tularemia, rickettsial diseases, ehr-lichiosis, leishmaniasis, and some cases of *Staphylococcus aureus* infection may be associated with leukopenia. Viral infections do not typically cause neutrophilia, but leukocytosis may be observed in the early phases of viral infection.

Box 1
Causes of neutrophilia

1. Secondary to other disease entities
   a. Infection
      i. Acute via release from marginated and storage pools
      ii. Chronic via increased myelopoiesis (eg, tuberculosis, fungal infection, chronic abscess, other chronic infections)
   b. Chronic inflammation
      i. Rheumatic disease: juvenile rheumatoid arthritis, rheumatoid arthritis, Still disease, and others
      ii. Inflammatory bowel disease
      iii. Granulomatous disease
      iv. Chronic hepatitis
   c. Cigarette smoking
   d. Stress
   e. Drug induced
      i. Corticosteroids
      ii. β-Agonists
      iii. Lithium
      iv. Recombinant cytokine administration
      v. Administration of inhibitors of adhesion molecules
   f. Nonhematologic malignancy
      i. Cytokine-secreting tumors (lung, tongue, kidney, urothelial tumors)
      ii. Marrow metastasis (myelophthisis)
   g. Marrow stimulation
      i. Hemolytic anemia, immune thrombocytopenia
      ii. Recovery from marrow suppression
      iii. Recombinant cytokine administration
   h. Postsplenectomy
2. Primary hematologic etiology
   a. Congenital neutrophilia
      i. Hereditary neutrophilia
      ii. Chronic idiopathic neutrophilia
      iii. Down syndrome
      iv. Leukocyte adhesion deficiency (LAD): LAD I and LAD II
   b. Acquired hematologic neoplasms
      i. Acute myelogenous leukemia
      ii. Myeloproliferative neoplasms
         1. Chronic myelogenous leukemia
         2. Polycythemia vera
         3. Essential thrombocytosis
         4. Idiopathic fibrosis

Infectious lymphocytosis (generally 20,000–50,000/μL small, mature-appearing lymphocytes) is mainly a disease of children. It may be related to coxsackievirus A or B6, echovirus, and adenovirus 12, and is rarely associated with splenomegaly or lymphadenopathy. Infection with Epstein-Barr virus (EBV) can cause atypical lymphocytosis (large and reactive lymphocytes with abundant basophilic cytoplasm) and lymphadenopathy. Human T-lymphotropic virus type 1 (HTLV-1) may produce a transient lymphocytosis (usually <20,000/μL) with fever, rash, and lymphadenopathy. In contrast to most other bacterial infections, pertussis (whooping cough) is frequently accompanied by lymphocytosis.

Noninfectious Causes of Leukocytosis

Leukocytosis can be caused by a variety of malignancies, chronic inflammatory conditions, medications, splenectomy, and in association with hemolytic anemia. Postsplenectomy leukocytosis may last weeks to months and has no clinical importance, but may lead to evaluation for other sources of abnormality. Patients with hemolytic anemia may experience a nonspecific increase in leukocyte production and release, in parallel with the increase in RBC production. Chronic smokers may exhibit a mildly increased WBC count that can persist for years.

Chronic inflammatory conditions, including rheumatoid arthritis, juvenile rheumatoid arthritis, and Still disease; inflammatory bowel disorders, such as Crohn disease and ulcerative colitis; vasculitides; granulomatous infections; and chronic hepatitis are often associated with leukocytosis. These processes are associated with increased expression of cytokines that stimulates neutrophil and monocyte production, but can deplete mature neutrophil pools over time. Leukocytosis associated with these inflammatory conditions is typically more modest than in acute infection or inflammation.

Neutrophilia may occur as a result of physical and emotional stress.[4,5] This transient increase in circulating neutrophils occurs within minutes of exercise, surgery, or other forms of stress, and typically reverses within hours of elimination of the trigger. Stress leukocytosis is presumed to be caused by catecholamine-induced demargination of neutrophils, and some cases can be prevented by pretreatment with β-adrenergic antagonists. Exercise-induced neutrophilia, however, is not blocked by propranolol, and may be due to redistribution of neutrophils from the lungs. An increased WBC count may be seen in the setting of acute myocardial infarction, but whether this is a risk factor for cardiac ischemia or a result of inflammation is unclear.[6]

Drug Effect

Medications commonly associated with leukocytosis include corticosteroids, lithium, and β-agonists.[7–9] Steroid administration typically leads to decreased egress from the circulation and increased demargination. Lithium causes neutrophilia by increasing the production of endogenous colony-stimulating factors (CSFs). The cytokines, granulocyte CSF (G-CSF) and granulocyte-macrophage CSF (GM-CSF), are routinely used to mobilize hematopoietic stem and progenitor cells for autologous and allogeneic hematopoietic stem cell transplantation,[10,11] and can cause pronounced neutrophilia if not appropriately managed. Mobilization is achieved within hours of administration of certain chemokines (interleukin-8),[12] small-molecule antagonists of the CXCR4 receptor (eg, AMD3100),[13] or a small-molecule antagonist of VLA-4 (BIO4860).[13,14]

Almost any kind of malignancy may cause leukocytosis, as tumors nonspecifically stimulate the production of leukocytes in bone marrow. Some tumors (eg, lung, tongue, kidney, bladder) can secrete G-CSF as an ectopic hematopoietic growth factor. Other tumors (eg, lung, stomach, breast) can cause a leukoerythroblastic reaction when they

spread to bone marrow.[15] Patients with Hodgkin lymphoma typically have mild to moderate neutrophilia, but neutrophilia can be associated with many nonhematologic malignancies.

Recovery of cell counts after marrow suppression, as in the case of chemotherapy, may cause rebound leukocytosis that can last for days to weeks. Similarly, hemolytic anemia and idiopathic thrombocytopenic purpura can result in generalized stimulation of the bone marrow and result in a so-called spillover leukocytosis.

Lymphocytosis

Lymphocytes normally represent 20% to 45% of circulating WBCs. Lymphocytosis conventionally refers to a lymphocyte count greater than 4000/μL, and is the second most common cause of leukocytosis (**Box 2**). The lymphocyte count increases in certain acute and chronic infections. Marked lymphocytosis is observed in individuals infected with pertussis ($\geq$40,000/μL), and lymphocyte counts greater than 100,000/μL indicate a poor prognosis. Chronic brucellosis[16] and syphilis infections[17] may occasionally cause an atypical lymphocytosis.

Viral infections may cause relative or absolute lymphocytosis, with or without neutropenia. Infectious mononucleosis is a self-limited infection caused by EBV infection of B lymphocytes. During the second week of illness, proliferating activated cytotoxic/suppressor T lymphocytes are seen in the peripheral blood as they attack and kill the infected B cells. Such large atypical lymphocytes are not unique to infectious mononucleosis, but can be seen in other viral infections. Infectious mononucleosis, which is

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Box 2
Causes of lymphocytosis

1. Infection
   a. Viral infection
      i. Epstein-Barr virus
      ii. Cytomegalovirus
      iii. Hepatitis
   b. Bacterial infection
      i. Pertussis
      ii. Bartonella
      iii. Tuberculosis
      iv. Syphilis
      v. Rickettsia
      vi. Babesia
2. Hypersensitivity reactions
   a. Serum sickness
   b. Drug hypersensitivity
3. Primary hematologic disease
   a. Chronic lymphocytic leukemia
   b. Monoclonal B-cell lymphocytosis
   c. Non-Hodgkin lymphoma

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most common in adolescents and young adults, typically presents with fever, sore throat, cervical lymphadenopathy, and splenomegaly. Cytomegalovirus (CMV) occasionally causes lymphocytosis with similar symptoms. Toxoplasmosis may cause similar atypical lymphocytosis with fever and lymphadenopathy. Other viral causes of lymphocytosis include infectious lymphocytosis and HTLV-1–related transient lymphocytosis.[18]

Relative, rather than absolute, leukocytosis occurs in infancy, and in association with some viral infections, connective tissue diseases, thyrotoxicosis, and Addison disease. Splenomegaly may cause relative lymphocytosis as a result of splenic sequestration of granulocytes.[19]

Monocytosis (>950/μL; **Box 3**) is commonly caused by bacterial infections, such as tuberculosis, subacute endocarditis, and brucellosis. Other infections include viral infections (eg, infectious mononucleosis), protozoal and rickettsial infections (eg, kala azar, malaria, Rocky Mountain spotted fever), and syphilis. Monocytosis can be seen during the recovery from neutropenia or an acute infection, autoimmune disease, and vasculitis (systemic lupus erythematosus, rheumatoid arthritis, ulcerative colitis, and inflammatory bowel disease). Sarcoidosis and lipid storage disease can be also heralded by monocytosis.[20]

Eosinophilia is defined as an absolute eosinophil count greater than 500/μL. The most common causes of eosinophilia are drug hypersensitivity and allergic conditions,

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Box 3
Causes of monocytosis

1. Infection
   a. Granulomatous disease (tuberculosis, fungal disease)
   b. Endocarditis
   c. Syphilis
2. Autoimmune diseases
   a. Lupus, rheumatoid arthritis
   b. Giant cell arteritis
   c. Vasculitis
3. Inflammatory bowel disease
4. Sarcoid
5. Malignancy
   a. Primary hematologic malignancy
      i. Chronic myelomonocytic leukemia
      ii. Acute myelomonocytic leukemia
      iii. Lymphoma
   b. Solid tumors
6. Neutropenia
   a. Associated with chronic neutropenia
   b. Recovery from marrow suppression
7. Postsplenectomy

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including asthma, hay fever, angioneurotic edema, urticaria, atopic dermatitis and eczema, eosinophilic esophagitis and enteritis, and others.

Eosinophils play an important role in the immune response to parasites. The most common parasitic infections in the United States that are associated with marked eosinophilia are parasites that cause visceral larva migrans by tissue invasion, such as *Toxocara canis* and *Toxocara cati*. Recovery from scarlet fever and some viral infections can also be associated with eosinophilia. Chlamydial infection causes an absolute increase in eosinophils, but generally does not result in leukocytosis. Eosinophilia is associated with dermatologic disorders, such as dermatitis herpetiformis, pemphigus, and erythema multiforme. Eosinophilia, together with basophilia, is seen in some cases of chronic myelogenous leukemia, and increasing counts may herald the onset of the blast phase of this disorder. Other intrinsic hematologic disorders that cause eosinophilia are discussed in the following paragraphs.

Basophilia, defined as a basophil count greater than $100/\mu L$, is seen in association with some allergic conditions and parasitic infections, but rarely leads to leukocytosis. Basophilia is most commonly seen in association with chronic myelogenous leukemia.

Nonmalignant Hematologic Disorders Associated with Leukocytosis

Familial neutrophilia, an autosomal dominant disorder of prominent leukocytosis (>20,000/μL), splenomegaly, and widened diploë of the skull, is caused by a mutation in the G-CSF receptor gene (CSF3R) (see **Box 1**).[21] Neutrophils in this disorder are functionally normal and the leukocytosis has no clinical consequences.

Chronic idiopathic neutrophilia (CIN) is marked by leukocytosis of 11,000/μL to 40,000/μL with a normal bone marrow. Smoking and obesity are significantly associated with CIN and may be causative, but CIN is unlikely to develop into a clinically recognizable myeloproliferative neoplasm, other than chronic myelogenous leukemia (CML).[22] A study with 20-year follow-up of patients with CIN indicated that no medical sequelae arise from the increased WBC count.[22]

Pelger-Huët anomaly (PHA) is characterized by mature neutrophils with bilobed nuclei, rather than the characteristic multilobed nuclear morphology. Because of their resemblance to old-fashioned eyeglasses, such granulocytes are described as pince-nez cells. PHA is caused by a mutation in the lamin B receptor gene.[23] Neutrophil function in PHA is normal, but automated cell counters may indicate a left-shifted WBC because they mistakenly classify the cells as immature granulocytes.

Acquired conditions that may be associated with bilobed granulocytes, so-called pseudo-PHA, include patients with myelodysplasia.[24] Treatment with colchicine, sulfonamides, ibuprofen, and valproate can cause reversible pseudo-PHA.[25] Because deficiencies of vitamin B_{12} or folate increase neutrophil nuclear lobation, these disorders may mask the diagnosis of PHA, but the aberrant neutrophil nuclear morphology returns with correction of the vitamin deficiency.

Transient myeloproliferative disorder (TMD) is seen in up to 10% of patients with Down syndrome (trisomy 21). TMD is characterized by peripheral blood leukocytosis in early infancy, and may include circulating myeloblasts in association with an accumulation of megakaryoblasts in the blood, liver, and marrow. TMD typically persists for several weeks and resolves spontaneously in most patients, but up to 30% of affected patients later develop acute megakaryoblastic leukemia.[26] TMD may also be seen in patients with trisomy 21 mosaicism who are phenotypically normal.

Patients with leukocyte adhesion deficiency (LAD) have persistent leukocytosis, defects in neutrophil activation, recurrent infections, and delayed separation of the umbilical stump. LAD is a congenital abnormality of leukocyte adhesion molecules. LAD I is attributable to the absence or marked reduction in the common β chain of

β2 integrins, resulting in loss of expression of leukocyte function-associated antigen 1 (LFA-1), the C3bi receptor, and GP150;95. Babies born with this disorder have persistent neutrophilia in the absence of clinical signs of infection, and increased susceptibility to infection. The diagnosis is confirmed by the absence of CD11b/CD18 on the patient's leukocytes by flow cytometry. In LAD II, neutrophils lack sialyl Lewis X, the ligand for L-selectin expressed on endothelial cells. Neutrophils appear morphologically normal, but are defective in chemotaxis, adherence, and phagocytosis.[27]

Familial cold urticaria is a rare autosomal dominant inflammatory disorder characterized by leukocytosis, episodic fevers, urticaria, rash, conjunctivitis, and muscle and skin tenderness with cold exposure. The rash consists of infiltrating neutrophils. The syndrome seems to be related to decreased levels of C1-esterase inhibitor and is associated with mutations in the CIAS1 gene on chromosome 1q.[28]

HEMATOLOGIC MALIGNANCIES

Leukocytosis is often the initial finding that leads to the diagnosis of a primary hematologic disorder, such as leukemia or a myeloproliferative neoplasm. Careful evaluation of the peripheral blood smear may suggest the underlying disorder and will help to generate the differential diagnosis. However, bone marrow evaluation for histology, flow cytometry, chromosome analysis, and molecular diagnostics are usually required to confirm the diagnosis of a primary hematologic disorder. Even when a pathognomonic finding is available from peripheral blood (eg, detection of the BCR-ABL rearrangement in CML), bone marrow evaluation provides crucial additional information (eg, the degree of marrow fibrosis).

Acute Myelogenous Leukemia

Acute leukemia arises from malignant transformation of an early hematopoietic progenitor cell (see **Box 1**). Instead of proliferating and differentiating normally, the affected cell gives rise to a clone of cells that fail to differentiate normally, and may proliferate in an uncontrolled fashion or fail to undergo programmed cell death, or apoptosis.

Because normal cellular elements in bone marrow may be decreased or absent, acute myelogenous leukemia (AML) often presents clinically as bone marrow failure. Symptoms include fever, infection, anemia, and bleeding or bruising, with corresponding signs on physical examination. Leukemic blasts may not be apparent in peripheral blood (so-called aleukemic leukemia) or may be abundant, ranging up to hyperleukocytosis. Abnormalities of WBCs are typically accompanied by variable degrees of anemia and thrombocytopenia. It is important to quickly recognize acute leukemias, as they may be associated with rapid life-threatening complications including bleeding, disseminated intravascular coagulopathy, leukostasis, brain infarction, and severe infections.

Morphology is an important clue to the nature of acute leukemia, but many cases cannot be definitively classified based on morphology alone. Myeloblasts are large cells with a high nuclear/cytoplasmic ratio; the nuclei may contain several distinct nucleoli, and a thin rim of cytoplasm may contain faint granularity. Bundles of cytoplasmic granules forming Auer rods are a pathognomonic finding in AML.

The diagnosis of AML requires confirmation by histochemical stains or immunophenotyping, and cytogenetic or fluorescent in situ hybridization (FISH) chromosome analysis of bone marrow specimens. More than half of all adults with AML exhibit characteristic nonrandom chromosomal abnormalities, and these anomalies are useful for categorizing patients with good, intermediate, or poor prognosis.[29]

The diagnosis of acute leukemia typically requires bone marrow aspiration and biopsy, usually from the posterior iliac crest. The bone marrow is usually hypercellular and contains at least 20% myeloblasts. Bone marrow should also be examined for fibrosis and dysplasia. However, the normal marrow architecture may be largely effaced, which makes it difficult to identify underlying hematologic disorders such as myelodysplasia or a myeloproliferative neoplasm.

Patients with AML require prompt diagnosis and therapy. WBC counts in excess of 100,000/μL constitute a medical emergency because of the risk of leukostasis (described earlier). Such patients may require therapeutic pheresis or emergent chemotherapy to reduce levels of circulating leukemic blasts and prevent life-threatening vascular complications. Patients with AML may require immediate trans-fusion of RBCs or platelets. In patients who are judged able to withstand the intensity of leukemia induction therapy, treatment with anthracyclines and cytarabine is usually administered. The resultant profound and prolonged cytopenias may result in infec-tious complications and threats to all bodily systems.

It is essential to promptly recognize and treat a distinct subset of AML known as acute promyelocytic leukemia (APL). APL is caused by rearrangement of the *retinoic acid receptor α* (*RARA*) gene to one of several partners. APL is unique among AML subsets because of its distinctive clinical presentation, therapy, and natural history. Prompt recognition and treatment of APL can avoid death from disseminated intravas-cular coagulation (DIC) or infection.[30,31] APL treatment uses all-*trans* retinoic acid (ATRA) in combination with cytotoxic chemotherapy or arsenicals, and has an excel-lent prognosis for cure if early death from DIC and infection can be avoided.

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is the most common childhood leukemia, but it is also seen in adults (although less commonly than AML) (see **Box 2**). Presentation in children may include lethargy, pallor, listlessness, fever, hepatosplenomegaly, and bruising. In adults, the clinical presentation is similar to AML. Most cases of ALL are of B-cell origin. Leukemic blasts in ALL exhibit a high nuclear/cytoplasmic ratio, fine chromatin, inconspicuous nucleoli, bluish cytoplasm, and no cytoplasmic granules. The diagnosis can be confirmed by histochemistry, immunophenotyping, karyotyping, and molecular diagnostics. Intensive induction therapy is usually followed by consol-idation therapy and prolonged maintenance therapy.

Chronic Leukemias

Patients with chronic leukemias typically present with less severe symptoms than those with acute leukemias. Chronic leukemia is usually diagnosed by incidental leukocytosis found on routine CBC. Chronic leukemias can be broadly divided into chronic lymphocytic leukemia and CML, depending on the cell of origin. The two cate-gories of chronic leukemia have different underlying molecular defects, clinical mani-festations, natural histories, and therapies.

CML (see **Box 1**) is a myeloproliferative neoplasm marked by clonal expansion of bone marrow myeloid precursor cells and increased numbers of circulating mature and immature myeloid cells. At presentation, CML must be distinguished from a leuke-moid reaction but, in contrast to a leukemoid reaction, CML is characterized by the presence of abnormalities of other blood cell lines (panmyelosis). Therefore, the peripheral blood smear in CML (but not the leukemoid reaction) may display concom-itant basophilia, eosinophilia, anemia, and thrombocytosis.

Most patients with CML are diagnosed incidentally on routine CBC, and many patients are asymptomatic for a long period. However, symptoms of CML include

fatigue, bleeding, weight loss, and abdominal discomfort or early satiety caused by splenomegaly; lymphadenopathy is uncommon.

The hallmark of CML is the Philadelphia chromosome (reciprocal translocation of chromosomes 9 and 22), which generates the BCR-ABL gene rearrangement that can be identified in peripheral blood by FISH or reverse transcriptase–polymerase chain reaction (RT-PCR). Previously a low leukocyte alkaline phosphatase (LAP) score was used as a diagnostic marker for CML, but this has been supplanted by direct molecular tests for BCR-ABL or the 9;22 chromosomal rearrangement.

The chronic phase of CML evolves into the accelerated phase, characterized by fever, sweats, weight loss, bone pain, bruising, and hepatosplenomegaly, and later, a blastic phase that resembles AML. The median time for transformation to blast phase is between 2 and 5 years. However, treatment of CML has been revolutionized by the development of targeted therapy with tyrosine kinase inhibitors (TKIs), which antagonize abnormal signal transduction signaling of the aberrant BCR-ABL protein. Treatment with TKIs is not curative, but survival of treated patients is significantly greater than for patients treated in the pre-TKI era.[32] Treatment with TKIs decreases the blastic transformation rates, perhaps because TKIs eliminate cells that are susceptible to blastic transformation. The blastic phase of CML remains very difficult to treat, even with TKIs and allogeneic stem cell transplantation.[33,34]

Chronic lymphocytic leukemia (CLL; see **Box 2**) results in accumulation of relatively mature-appearing lymphocytes in bone marrow, peripheral blood, lymph nodes, spleen, and other organs. Molecular defects in the normal processes of apoptosis cause accumulation of these malignant lymphocytes. Immunity is decreased because the malignant lymphocytes exhibit impaired immune function.

The lymphocytes in CLL generally appear mature, with condensed nuclei and a thin rim of bluish cytoplasm. These lymphocytes are fragile, and result in so-called smudge cells in the peripheral smear. CLL may be often accompanied by anemia and/or thrombocytopenia caused by impaired bone marrow production, splenic sequestration, or immune destruction. The diagnosis of CLL is established definitively by flow cytometry, which demonstrates a clonal population of lymphocytes that coexpress markers of both B cells (eg, CD19) and T cells (eg, CD5). Evaluation of the bone marrow can define the degree and pattern of bone marrow involvement and the status of other cellular lineages. In the absence of constitutional symptoms (fever, sweats, weight loss), critical cytopenias, troublesome adenopathy, or organ dysfunction, CLL may be managed by careful observation.

The group of BCR-ABL–negative myeloproliferative neoplasms (MPNs) includes chronic myelomonocytic leukemia (CMML), polycythemia vera (PV), myelofibrosis (MF), and essential thrombocythemia (ET). Because all of these entities may present with leukocytosis, distinguishing between them can be difficult, and may require special laboratory studies and bone marrow examinations.[35]

Although superficially resembling CML in its clinical and morphologic presentation, CMML is considered a separate entity because of its particular clinical, therapeutic, and prognostic aspects. CMML is manifest as a myeloproliferative neoplasm that involves the monocytic series and dysplasia of the erythroid-megakaryocytic series. Patients with CMML are older (65–70 years) than most patients with CML. Cytogenetics are usually normal or trisomy 8, and patients with CMML have RAS mutations in 40% to 60% of cases, whereas JAK2 mutation is rare (4%).[36]

PV, MF, and ET are associated with activating mutations in the JAK2 gene (PV: 65%–97%; ET: 23%–57%; MF: 35%–57%).[37] PV usually is characterized by deregulated and excessive production of RBCs, but increased WBC and platelet counts may also be evident. Symptoms resulting from hypervolemia and hyper viscosity, such as

headache, dizziness, visual disturbances, and paresthesias, are sometimes present. Less frequently, patients with PV present with myocardial infarction, stroke, venous thrombosis, and congestive heart failure. Overall survival is generally long (10–20 years).[38]

MF is a bone marrow disorder in which fibroblasts replace normal elements of the marrow. Patients with myelofibrosis are usually 50 years or older and have a median survival of less than 10 years. As bone marrow fibrosis develops, patients can develop leukocytosis, although decreased WBC, RBC, and platelet counts are more common. Patients are asymptomatic early in the course of the disease and are usually diagnosed incidentally based on changes in blood cell counts. Symptomatic patients have fatigue, shortness of breath, weight loss, bleeding, or abdominal discomfort related to splenomegaly. Acute leukemia can develop over time and, when it occurs, usually progresses rapidly.

Leukocytosis is also found in patients with ET. Although increased platelet counts occur in all myeloproliferative disorders, ET is distinguished by the singular prominence of platelets. This diagnosis is one of exclusion, in which t(9;22) and bone marrow fibrosis are absent. It is also important to exclude secondary thrombocytosis caused by nonmarrow disorders (eg, iron deficiency or bleeding). Most patients with ET are asymptomatic and require little, if any, therapy, but some patients develop thrombosis or hemorrhage secondary to increased numbers of dysfunctional platelets.

Several primary hematologic disorders may affect eosinophils. Hypereosinophilic syndrome (HES), in which eosinophil counts of more than 1500/μL persist for at least 6 months, is associated with infiltration of essential organs, such as the heart and the nervous syndrome. Some patients with HES have rearrangements of the *PDGFRA* and *FIP1L* genes that create an activated tyrosine kinase.[39] Patients may respond to steroids, cytotoxic agents, imatinib (especially in patients with *PDGFRA-FIP1L* rearrangements), or mepolizumab (anti–interleukin-5 monoclonal antibody).[40] Untreated, HES inevitably leads to progressive disability and death. Eosinophilic leukemia exhibits accumulation of incompletely differentiated eosinophils.

DIAGNOSTIC WORKUP OF LEUKOCYTOSIS

Leukocytosis is most commonly the result of acute or chronic infection, inflammation, nonhematologic malignancy, or medications. In such clinical settings, leukocytosis represents an appropriate physiologic response of the hematopoietic system to stress. These diagnoses can generally be identified by careful clinical history and physical examination, examination of the peripheral blood smear, and other laboratory and imaging studies. In such settings, direct evaluation of the bone marrow is rarely warranted, unless it is to document infection involving the bone marrow itself.

However, leukocytosis in the absence of such signs and symptoms, coincident anemia or thrombocytopenia, or evidence of a leukoerythroblastic reaction should prompt consideration of bone marrow examination. These findings may point toward an intrinsic hematologic disorder, such as an MPN, leukemia, or lymphoma, or may suggest metastatic cancer or fibrosis involving the bone marrow.

Medical History

A careful history is essential for accurate diagnosis of the cause of leukocytosis. Symptoms such as fever, cough, gastrointestinal symptoms, rash, or swelling may suggest an underlying infection. Infections may present acutely, but longer-term complaints such as fever, rash, or joint pain may broaden the differential diagnosis to include chronic infections, inflammation, or autoimmune diseases. Weight loss, fatigue, and

night sweats should prompt consideration of an underlying hematologic or nonhematologic malignancy. Medications such as corticosteroids or epinephrine cause a transitory increase in neutrophil count, and a rebound from recent treatment with chemotherapy, especially if therapeutic cytokines have been used, may account for leukocytosis. History of cigarette smoking and exercise should be defined. In children, sickle cell disease should be considered, and in infants the transient leukemoid reaction seen in Down syndrome or LAD syndromes should be considered.

Physical Examination

A careful examination for infection, including cellulitis, otitis, pharyngitis, pneumonia, urinary tract infection, or abscesses should be sought. The heart and extremities should be carefully examined for stigmata of infective endocarditis. Lymphadenopathy or hepatosplenomegaly points toward a possible viral cause, but may also reflect an underlying malignancy. Tender or swollen joints may indicate juvenile rheumatoid arthritis, septic arthritis, or systemic lupus erythematosus. Stigmata of Down syndrome may explain leukocytosis.

Laboratory Tests

CBC

A confirmatory CBC with differential count should be obtained, and previous CBCs can document the duration of leukocytosis. The nature of the increased cells, that is, granulocytes versus lymphocytes, will often set the direction of further evaluation. It is critical to personally examine the peripheral blood smear. The blood smear in bacterial infection may demonstrate a left shift of granulocytes, accompanied by Döhle bodies, toxic granulations, or vacuolization. Immature granulocyte forms, such as myeloblasts, promyelocytes, and myelocytes, should prompt consideration of acute or chronic leukemias. Pelger-Huët cells or other evidence of granulocyte dysplasia may suggest underlying myelodysplasia, and an increased lymphocyte count accompanied by smudge cells suggests CLL.

Abnormalities of other cellular lineages may provide important clues about the underlying diagnosis. Schistocytes may point toward disseminated intravascular coagulopathy, and a leukoerythroblastic appearance with anemia or thrombocytopenia may suggest a marrow infiltrative disorder, such as cancer, infection, or fibrosis. Anemia with spherocytosis and thrombocytopenia may suggest extravascular hemolysis, as is seen in lymphoma. RBC inclusions may point toward malaria or other intracellular parasites, whereas target cells or sickle cells may indicate an underlying hemoglobinopathy. Recovering or stressed marrow may exhibit an increased monocyte count. Increased numbers of eosinophils and/or basophils may suggest CML.

Other laboratory studies

No single panel of laboratory studies is useful in evaluating all patients with leukocytosis. Thus, laboratory studies should be selected to clarify and perhaps broaden the differential diagnosis.

Liver function tests may point to a possible viral or bacterial infection. Appropriate cultures of blood, urine, stool, or throat may define the underlying disorder. Other useful studies may include Mono spot, heterophil antibodies, EBV, or CMV titers to evaluate infectious mononucleosis.

Uric acid and lactate dehydrogenase are often increased in leukemias and lymphomas. Serologic studies, such as antinuclear antibody, may point toward a rheumatologic origin. LAP was used previously to distinguish infection (increased LAP score) from CML (decreased LAP score), but this has largely been supplanted by

more precise testing. RT-PCR performed on peripheral blood for *BCR-ABL* and *JAK2* mutation may document CML or other MPNs, and FISH or cytogenetics can demonstrate the t(9;22) found in CML.

Radiologic examination, such as chest radiographs, may indicate pneumonia, tuberculosis, or other infections. Ultrasonography, computed tomography (CT), positron-emission tomography combined with CT, and other imaging modalities may demonstrate abscesses, tumor masses, or even bone marrow infiltration.

SUMMARY

Leukocytosis is one of the most common laboratory findings in medicine, and represents one of the most frequent sources of requests for hematologic consultation. Because the differential diagnosis potentially encompasses the entirety of medical disorders, the consulting hematologist must make a thoughtful evaluation. The evaluation requires an attentive history, careful physical examination, meticulous review of the CBC and peripheral blood smear, and judicious application of laboratory and radiologic testing. The resultant findings may prompt bone marrow aspiration and biopsy to document cellular morphology and immunophenotype, culture for infectious agents, chromosome analysis, and molecular studies. The results of this evaluation should indicate the appropriate treatment for the underlying disorder.

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