White Blood Cell Disorders
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KEY POINTS

- White blood cell disorders are the result of cell overproduction, underproduction, or dysfunction.
- Hematologic malignant diseases have variable initial presentations and significant associated complications.
- Rapid evaluation and intervention are essential to minimize morbidity and mortality in the immunocompromised patient.

EPIDEMIOLOGY

The National Cancer Institute estimated that approximately 137,260 new cases and 54,020 deaths from hematologic malignant diseases (leukemias, lymphomas, and plasma cell disorders) occurred in 2010. On January 1, 2007, approximately 908,512 men and women living in the United States had a history of hematologic malignant disease. In adults, non-Hodgkin lymphomas and chronic lymphocytic leukemia are the most common of these diseases. Of a total of 26,446 childhood cancers (age 1 to 19 years) diagnosed in the United States from 2001 to 2003, leukemias were the most common (26.3%). The lymphoid leukemias were the type with the highest incidence. Lymphomas, comprising 14.6% of new childhood malignant diseases, were the third most common cancers. A history of malignant disease is a common feature in the emergency department (ED) patient population. In a retrospective review of 5640 patients in a community teaching hospital with an annual ED census of 31,000, cancer history was identified in 5% of patients. Ten percent of patients with oncology-related visits died during the admission, and 48% died within 1 year of the ED visit.

PATHOPHYSIOLOGY

White blood cells (WBCs), or leukocytes, are the primary cells responsible for the inflammatory and immune response. WBCs include granulocytes (neutrophils, eosinophils, basophils) and mononuclear cells (T and B lymphocytes, monocytes). These cells are all produced from a common stem cell in the bone marrow, and they differentiate through various cytokines including colony-stimulating factors and interleukins. Normal blood leukocyte counts are 4.34 to 10.8 × 10⁹/L, with neutrophils representing 45% to 74% of cells, bands representing 0% to 4%, lymphocytes representing 16% to 45%, monocytes representing 4% to 10%, eosinophils representing 0% to 7%, and basophils representing 0% to 2%. WBC disorders are the result of cell overproduction, underproduction, or dysfunction (Box 203.1). The WBC count with differential lacks specificity and sensitivity but is the most frequent laboratory test ordered by emergency physicians.

LEUKOPENIA

Leukopenia, or a WBC count less than 1.5 × 10⁹/L, is most clinically relevant with significant neutropenia and its complications (primarily increased risk of infection, further outlined in Chapter 201). Although neutropenia is most common in patients with bone marrow suppression secondary to chemotherapy, Box 203.2 outlines a differential diagnosis of certain infections that characteristically manifest with neutropenia. Lymphocytopenia is a nonspecific finding that is present in many bacterial, fungal, viral, and protozoan infections.

LEUKOCYTOSIS

Leukocytosis, or an increased number of WBCs, is defined as an elevation in the total number of circulating WBCs greater than 2 standard deviations above the age-based mean circulating WBC count. This disorder is most commonly secondary to infections or systemic stressors; however, an increase in a subset of WBCs (neutrophilia, monocytosis, lymphocytosis, eosinophilia, or basophilia) may guide the differential diagnosis. Bacteria are the culprit in two thirds of infection-related cases of neutrophilia. Box 203.3 outlines infectious causes of lymphocytosis, with Bordetella pertussis being the rare bacterial exception. Eosinophilia is classically caused by multicellular parasites that invade tissue, most commonly seen in invasive parasitic disease, but it may also be seen in protozoan and fungal infections.

MORPHOLOGIC CHANGES

In addition to altered numbers, changes in cellular morphology found in a peripheral blood smear may aid in the diagnosis. A left shift (or greater percentage of immature cells, such as metamyelocytes) may be present in severe infection. Intracellular abnormalities including toxic granulations,
BOX 203.1 Differential Diagnosis of White Blood Cell Disorders by Pathogenesis

Overproduction
*Stress (Infections, Inflammation)*
- Corticosteroids
- Granulocyte colony-stimulating factor
- Acetylcholine
- Adrenergic agents
- Heparin
- Lithium
- Histamine
- Lead
- Iron

*Neoplastic Disease*

Primary Hematologic
- Myelodysplastic syndromes
- Acute leukemias
- Chronic leukemias
- Chronic lymphocytic leukemia
- Hairy cell leukemia
- Large granular lymphocytic leukemia
- Non-Hodgkin lymphoma

Cancers Metastatic to Bone
- Most commonly breast, lung, prostate, and lymphomas

Underproduction
*Drug or Toxin Suppression*
- Cancer chemotherapy
- Phenytoin
- Penicillins
- Sulfas

*Aplastic Anemia*

*Malignant Disease (Leukemia, Myelodysplastic Syndrome)*

*Vitamin B₁₂ or Folate Deficiency*

*Dysfunction*
*Increased Splenic Sequestration*
- Cirrhosis
- Gaucher disease

*Diabetes Mellitus*
- Impaired polymorphonuclear neutrophil function

*Chronic Renal Failure*
- Impaired polymorphonuclear neutrophil and lymphocyte function

*Drugs*
- Corticosteroids


BOX 203.2 Infections That May Cause Neutropenia in the Normal Host

*Bacterial*
- Salmonellosis
- Tularemia
- Brucellosis
- Rickettsial disease (Rocky Mountain spotted fever)
- Miliary tuberculosis

*Viral*
- Measles
- Varicella (chickenpox)
- Rubella
- Influenza
- Infectious hepatitis
- Yellow fever
- Sandfly fever
- Human immunodeficiency virus infection
- Colorado tick fever
- Dengue fever

*Protozoan and Parasitic*
- Malaria
- Kala-azar
- Relapsing fever


BOX 203.3 Infections That May Cause Lymphocytosis

*Acute Infection*
- Pertussis
- Infectious mononucleosis
- Infectious hepatitis
- Acute infectious lymphocytosis
- Toxoplasmosis
- Cytomegalovirus

*Chronic Infection*
- Tuberculosis
- Brucellosis
- Syphilis
- Rickettsial disease

cytoplasmic vacuolization, and Dohle bodies are likely secondary to infection (Fig. 203.1). 6

WHITE BLOOD CELL MALIGNANCY

Although WBC disorders have a vast differential diagnosis, the remainder of this chapter focuses on hematologic malignant diseases. Leukemias, lymphomas, and plasma cell disorders are the main general categories of these malignant diseases.

Leukemias are a result of failure of differentiation of hematopoietic precursor cells that leads to unchecked proliferation of blasts, either immature myeloid or lymphoid cells, which impede the normal manufacturing of red blood cells, WBCs, and platelets in the bone marrow. Anemia, bleeding, and infection are a result of decreased normal cell production. Eventually, blasts multiply and migrate throughout other hematopoietic organs including the spleen and lymph nodes. In acute leukemias, WBC counts vary greatly (25% of patients have counts <5000/microliters, 25% have counts >50,000/microliters, and 50% have counts between 5000 and 50,000/microliters), but anemia, thrombocytopenia, and blasts are common. Bone marrow aspiration and biopsy are used to diagnose leukemias definitively.

Lymphomas are a vast group of malignant diseases defined by clonal proliferation of malignant lymphocytes. The World Health Organization lymphoma classification defined 27 types of lymphomas categorized primarily by the primary clonal cells: B cells, T cells, or natural killer cells. Lymphocytosis and varied characteristic cells are present on a peripheral blood smear. Lymph node and bone marrow biopsy also aid in the diagnosis. Monoclonal proliferation of immunoglobulin-secreting plasma cells characterizes plasma cell disorders. These conditions include multiple myeloma, monoclonal gammopathies, Waldenström macroglobulinemia, heavy-chain diseases, cryoglobulinemia, and primary amyloidosis. These diseases are diagnosed by using serum or protein electrophoresis and bone marrow analysis.

Acute Myelogenous Leukemia

Patients with leukemia present with signs and symptoms secondary to the invasion of other organs by leukemic cells and decreased production of normal hematopoietic cells. Fever, malaise, and a viral-like syndrome are common presenting symptoms. Diffuse bony tenderness, as a result of expansion of the intramedullary space or periosteal infiltration by leukemic cells, is the initial symptom in 25% of patients. 9

Acute myelogenous leukemia (AML) typically affects all three cell lines and results in anemia, thrombocytopenia, and neutropenia. Pallor, dyspnea, and chest pain reflect anemia, whereas petechiae, ecchymosis, and excessive bleeding are a result of thrombocytopenia. One third of patients will have significant infections on diagnosis. 10 Splenomegaly occurs in up to 50% of patients, and lymphadenopathy is rare. 9

AML has several skin manifestations. Raised, nontender plaques or nodules (leukemia cutis) are manifest in many forms of leukemia, but they are most commonly seen in AML (Fig. 203.2). 11 Tender, pseudovesicular, erythematous plaques are a characteristic feature of Sweet syndrome, which may precede the diagnosis of AML by months (Fig. 203.3). Gingival hyperplasia may also be present (Fig. 203.4).
CHAPTER 203  WHITE BLOOD CELL DISORDERS

CHRONIC MYELOGENOUS LEUKEMIA
Thirty percent to 50% of patients diagnosed with chronic myelogenous leukemia are asymptomatic. Splenomegaly is present in 50% to 60%, and hepatomegaly occurs in 10% to 20% of new cases. Lymphadenopathy is rare.

NON-HODGKIN LYMPHOMA
Presentation of non-Hodgkin lymphoma is extremely variable, but patients most commonly seek medical evaluation for incidental painless, firm cervical, axillary, or inguinal adenopathy. Chest pain, cough, superior vena cava syndrome, abdominal pain, back pain, spinal cord compression, and symptoms of renal insufficiency may be present. Fevers, night sweats, and weight loss are also common symptoms.

HODGKIN LYMPHOMA
Fever, night sweats, and weight loss are the classic “B” symptoms associated with Hodgkin lymphoma. Other classic signs are systemic pruritus and painful lymphadenopathy after drinking alcohol. Painless, rubbery, supradiaphragmatic lymphadenopathy, particularly of the neck and supraclavicular nodes, is common. Less than 10% of patients will have a subdiaphragmatic presentation.

PLASMA CELL DISORDERS
Fatigue and bone pain are the most common presenting symptoms of multiple myeloma. Pain may be secondary to characteristic lytic lesions or pathologic fractures (Fig. 203.5). Focal weakness or paresthesias may be secondary to nerve root or spinal cord compression from extramedullary expansion of bony lesions.

DIFFERENTIAL DIAGNOSIS, MEDICAL DECISION MAKING, AND TREATMENT
Once the diagnosis of a hematologic malignant disease is suspected, laboratory evaluation should be performed, including a complete blood cell count with manual differential, peripheral blood smear, chemistry studies (including uric acid,
creatinine, potassium, phosphorus, and calcium), coagulation factors, and blood type and screen. If the patient is febrile, blood cultures (aerobic, anaerobic, and fungal) should also be obtained, and empiric antibiotics should be initiated early because many of these patients have functional neutropenia, even in the setting of normal neutrophil count, and are at high risk of bacteremia or sepsis. 

Diagnostic imaging should be ordered based on the fociality of patients’ symptoms, but a chest radiograph is a general starting point to evaluate any of the intrathoracic complications associated with these malignant diseases. An electrocardiogram should be performed to evaluate for evidence of electrolyte abnormalities.

Patients presenting with hyperleukocytosis (an extreme elevation of the blast count or WBC count >100,000/mm$^3$) and many different symptoms affecting multiple organ systems are at an increased risk of hyperviscosity syndrome (see Box 203.5), a medical emergency with mortality rates as high as 40%. Metabolic and electrolyte abnormalities are common. The most serious complication is tumor lysis syndrome, a result of the massive cell lysis, which releases intracellular urate, phosphate, and potassium (please refer to Chapter 201 for details on tumor lysis syndrome).

**CARDINAL PRESENTATIONS AND COMPLICATIONS OF PATIENTS WITH KNOWN WHITE BLOOD CELL CANCER**

Abdominal pain, dyspnea, fever, and malaise are all key chief complaints that require a comprehensive ED evaluation in patients with WBC disorders. Box 203.4 lists the differential diagnosis of these complaints.

**ABDOMINAL PAIN**

Gastrointestinal symptoms are the most common chief complaints of patients with cancer who present to the ED. Immunosuppressed patients represent a diagnostic challenge, because classic examination findings of an acute abdomen may be replaced by nonspecific signs or systems such as tachycardia, hypotension, and altered mental status.

In addition to disorders present in the immunocompetent host, disorders secondary either to the malignant disease or to the therapy used to combat it should be considered. Opportunistic infections, intestinal obstruction, perforation, typhlitis, and venoocclusive disease of the liver (Budd-Chiari syndrome) should be considered in the differential diagnosis of...
a patient with cancer who has an acute abdomen. In a retrospective series of patients with acute leukemia who developed severe abdominal infections during chemotherapy-induced neutropenia, 68% presented with enterocolitis (primarily bacteremia, but also fungal and viral infections). A broad diagnostic strategy, including abdominal diagnostic imaging (computed tomography [CT] or ultrasound, or both), is usually necessary in the thorough evaluation of these patients.

Typhlitis, or neutropenic enterocolitis, is a necrotizing inflammation of the ascending colon or cecum that is a common cause of the acute abdomen in a neutropenic patient (Fig. 203.6). Although the incidence varies (from 0.8% to 26%), typhlitis has a mortality rate of 50% and higher. The pathogenesis is unclear, but theories have implicated failed mucosal integrity secondary to chemotherapy or the migration of bacteria causing bowel necrosis and hemorrhage secondary to the effects of neutropenia. Several case reports have described typhlitis as a presentation of acute leukemia. Signs and symptoms vary. In a retrospective case review of 10 patients, all presented with fever, and some had abdominal pain (most commonly right lower quadrant), nausea, diarrhea, and hypotension. CT imaging shows bowel wall thickening but is not specific. Therefore, CT is recommended in addition to ultrasound, to assess potential complications, including colonic wall hemorrhage, pneumatosis intestinalis, pneumoperitoneum, and abscesses, more thoroughly.

Broad-spectrum antibiotics (covering enteric gram-negative organisms, Pseudomonas, and anaerobes including Clostridium difficile), bowel rest, surgical evaluation, and supportive care are recommended.

Hepatic venous outflow obstruction caused by thromboses, or Budd-Chiari syndrome, results from a hypercoagulable state or direct tumor invasion of the hepatic venous system. Venous stasis and hepatic congestion lead to cell death and eventual liver failure. Symptoms include ascites, hepatomegaly, abdominal pain, jaundice, and, in severe cases, variceal bleeding and portal hypertension. Ultrasound scanning with Doppler is the initial imaging modality of choice; it has a sensitivity of more than 85%, but CT and magnetic resonance imaging are alternatives. The initial management strategy consists of sodium restriction, diuretics, anticoagulation, and periodic paracentesis. Portosystemic shunting or liver transplantation is indicated for severe forms of Budd-Chiari syndrome.

DYSPNEA

Patients presenting to the ED with dyspnea should be approached with a rapid assessment of respiratory status and should be given immediate resuscitative care in the form of supplemental oxygen, assisted ventilation, or intubation with mechanical ventilation. Despite this initial universal approach to the dyspneic patient, investigation of the broad differential diagnosis is essential to formulating an emergency management plan.

Acute respiratory failure is the most common cause of admission to the intensive care unit (ICU) in patients with cancer, and it has an incidence of 10% to 50% and an overall mortality rate of 50%. Patients with leukemia and lymphoma have a higher incidence of respiratory insufficiency as the cause of ICU admission than do patients with solid tumors.

Common causes of acute respiratory failure in these patients include pulmonary infections (pneumonia), cardiogenic or noncardiogenic pulmonary edema, antineoplastic (chemotherapy or radiation) therapy-induced lung injury, venous thromboembolism, diffuse alveolar hemorrhage (DAH), airway obstruction, and underlying disease progression.

Pneumonia is the most common cause of respiratory failure in patients with hematologic malignant diseases. Streptococcus pneumoniae and Haemophilus influenzae are the most
common organisms in patients with leukemia and myeloma (impaired B-cell immunity). Patients with Hodgkin lymphoma (impaired T-cell immunity) are more likely to be infected with *Pneumocystis jiroveci*, mycobacteria and fungi, and viruses (including cytomegalovirus and herpes simplex virus). Presentation may be atypical. Although fever is common, cough and sputum are not, and findings on chest radiography may be normal. Chemotherapy-induced neutropenia can give rise to infection with *Staphylococcus aureus*, gram-negative bacilli (*Pseudomonas* and *Klebsiella*), and opportunistic fungi (*Aspergillus*). Dehydration, malnourishment, prolonged bed rest, and central nervous system metastasis predispose oncologic patients to increased aspiration risk. Pulmonary edema may be cardiogenic, noncardiogenic, or a combination thereof because of several inciting events, including the use of cardiotoxic chemotherapeutic agents, infection, radiation, or transfusions. These patients are at a high risk of developing acute respiratory distress syndrome (ARDS).

Chemotherapy- and radiation-induced lung injury comprises another syndrome that may manifest with exertional dyspnea, low-grade fevers, and a nonproductive cough during or up to several months after treatment. The various diagnoses include interstitial pneumonitis, acute lung injury, ARDS, capillary leak syndrome, organizing pneumonia, hypersensitivity reaction, bronchospasm, and DAH. On examination, bilateral inspiratory crackles may be auscultated, and diffuse or patch ground-glass opacities are seen on chest radiography and CT. Each syndrome requires a multipronged approach, but cessation of the culprit chemotherapeutic agent and treatment with systemic corticosteroids are general management principles.

Venous thromboembolism (deep venous thrombosis or pulmonary embolism) is an important cause of morbidity and mortality in patients with cancer and may be a predictor of worse overall prognosis. Chemotherapeutic agents, intrinsic procoagulant tumor activity, indwelling catheters, immobilization, and surgery are risk factors for venous thromboembolism in oncologic patients. Ten percent of patients with lymphoma develop venous thromboembolism. Presenting symptoms of dyspnea, pleurisy, and palpitations and signs of tachypnea, hypoxia, and dysrhythmias should prompt a thorough evaluation for venous thromboembolism.

DAH is common in patients with leukemia or multiple myeloma, after bone marrow transplantation, and in patients with thrombocytopenia (platelets < 50,000/mm^3^). Total body irradiation, thoracic irradiation, and increased age are all risk factors for DAH. Patients present with progressive dyspnea, cough, and fever but rarely hemoptysis. Chest radiography may show diffuse interstitial and alveolar infiltrates, and the diagnosis is confirmed by bronchoscopy. Supportive therapy includes corticosteroids, platelet transfusions, and mechanical ventilator support.

Transfusion-related acute lung injury may develop in those patients receiving red blood cells, platelets, or fresh frozen plasma. Patients develop fever, hypotension, hypoxemia, pulmonary hypertension, and noncardiogenic pulmonary edema within 6 hours of transfusion. Treatment is supportive and often requires ventilatory support.

Airway obstruction may be secondary to locally advanced tumors in the airway or metastatic lesions to the mediastinum or tracheobronchial tree. Lymphoma may develop mediastinal masses that may cause stridor, dyspnea, hemoptysis, or cough.

Chest radiography, CT, and bronchoscopy are used in combination to establish a diagnosis and guide therapy. Definitive airway management is difficult but may be essential in these patients. Eventual treatment may consist of stents, lasers, radiation therapy, or chemotherapy.

**PAIN**

The most common complaint of patients with cancer who present to the ED is pain, with nausea or vomiting and weakness a close second and third most frequent chief complaints. Although pain is nonspecific, the ED physician needs to be aware of critical, life-threatening diagnoses that may manifest with pain.

Hypercalcemia may occur in up to 30% of patients with cancer, and they may present with vague symptoms of nausea, vomiting, abdominal pain, or myalgias. Hypercalcemia may lead to progressive neurologic symptoms, coma, renal failure, and arrhythmias. In multiple myeloma, hypercalcemia results from bone osteoclastic bone resorption. Lymphomas and myelomas hydroxylate vitamin D into 1,25-dihydroxyvitamin D (1.25(OH)2D), the active form of vitamin D, thus enhancing intestinal absorption of vitamin D and resulting in hypercalcemia. This diagnosis is critical in this patient population because approximately 50% of these patients will die within 30 days. The diagnosis is best made by using ionized calcium, and an electrocardiogram may show a shortened QT interval. The cornerstone of management is aggressive intravenous and oral hydration. Once volume repletion is achieved, loop diuretics are used for calcium excretion. Bisphosphonates, calcitonin, and steroids are other adjuncts, depending on the response to treatment and the primary cause of the elevated calcium concentration. Please refer to Chapter 201 for further details on hypercalcemia.

Acute blood hyperviscosity results from elevations of serum proteins (hyperviscosity syndrome) or WBCs (hyperleukocytosis) in the blood circulation. Leukocytosis and leukostasis (Fig. 203.7) have mortality rates that range from 20%
to 40%, and these conditions therefore represent an emergency diagnosis. Boxes 203.5 and 203.6 outline the presentations and management of both conditions.

**NEXT STEPS OF CARE: ADMISSIONS (INPATIENT AND OUTPATIENT)**

Overall patient disposition is based on clinical assessment, the ability to follow-up with a primary care physician or oncologist, and the patient’s home environment.

A patient with a new diagnosis of malignant disease may require an in-depth work-up that may be more rapidly facilitated by admission and coordination between oncology staff and primary care physicians.

For patients with a known cancer diagnosis, positive pressure isolation rooms should be considered in patients with significant neutropenia, in bone marrow transplant recipients, or in patients with other high-risk immunocompromised states (after intensive chemotherapy or solid organ transplantation). Intensive care monitoring should be reserved for patients who are critically ill, usually from complications of immunocompromise or chemotherapy.

**SUGGESTED READINGS**


**REFERENCES**

*References can be found on Expert Consult @ www.expertconsult.com.*
REFERENCES