9 - Hematology and Oncology

Chapter 104. Approach to the Patient With Anemia

Introduction

Red blood cell (RBC) production (erythropoiesis) takes place in the bone marrow under the control of the hormone erythropoietin (EPO). Juxtaglomerular cells in the kidney produce EPO in response to decreased O_2 delivery (as in anemia and hypoxia) and increased levels of androgens. In addition to EPO, RBC production requires adequate supplies of substrates, mainly iron, vitamin B_{12}, and folate. Vitamin B_{12} and folate are discussed in Ch. 4; iron is discussed on pp. 53 and 924.

RBCs become senescent after about 120 days. They then lose their cell membranes and are largely cleared from the circulation by the phagocytic cells of the spleen, liver, and bone marrow. Hb is broken down in these cells and in hepatocytes primarily by the heme oxygenase system with conservation (and subsequent reutilization) of iron, degradation of heme to bilirubin through a series of enzymatic steps, and reutilization of protein. Maintenance of a steady number of RBCs requires daily renewal of 1/120 of the cells; immature RBCs (reticulocytes) are continually released and constitute 0.5 to 1.5% of the peripheral RBC population.

Low levels of androgens leading to decreased EPO levels in women and girls and in elderly patients can predispose to anemia, as does the decline in the capacity of bone marrow to produce RBCs. With aging, Hb and Hct decrease slightly, but not below normal values. In women, other factors that frequently contribute to lower levels of RBCs include cumulative menstrual blood loss and increased demand for iron due to multiple pregnancies.

Etiology of Anemia

Anemia is a decrease in the number of RBCs, Hct, or Hb content.

The RBC mass represents the balance between production and destruction or loss of RBCs. Thus, anemia can result from one or more of 3 basic mechanisms (see Table 104-1):

[**Table 104-1.** Classification of Anemia by Cause]

• Blood loss

• Deficient erythropoiesis

• Excessive hemolysis (RBC destruction)

Blood loss can be acute or chronic. Anemia does not develop until several hours after acute blood loss, when interstitial fluid diffuses into the intravascular space and dilutes the remaining RBC mass. During the first few hours, however, levels of polymorphonuclear granulocytes, platelets, and, in severe hemorrhage, immature WBCs and normoblasts may rise. Chronic blood loss results in anemia if loss is more rapid than can be replaced or, more commonly, if accelerated erythropoiesis depletes body iron stores (see p. 924).

Deficient erythropoiesis (see p. 924) has myriad causes. Complete cessation of erythropoiesis results in a decline in RBCs of about 7 to 10%/wk (1%/day). Impaired erythropoiesis, even if not sufficient to decrease the numbers of RBCs, often causes abnormal RBC size and shape.

Excessive hemolysis (see p. 934) can be caused by intrinsic abnormalities of RBCs or by extrinsic factors, such as the presence of antibodies on their surface, that lead to their early destruction. An enlarged spleen sequesters and destroys RBCs more rapidly than normal. Some causes of hemolysis deform as well as destroy RBCs. Excessive hemolysis does not normally decrease reticulocyte production

unless iron or other essential nutrients are depleted.

Evaluation of Anemia

Anemia is not a diagnosis; it is a manifestation of an underlying disorder. Thus, even mild, asymptomatic anemia should be investigated so that the primary problem can be diagnosed and treated.

Acute or chronic blood loss is the first consideration. The diagnosis usually is based on history, examination, and a stool test for occult blood. Further testing for occult bleeding is sometimes necessary.

If blood loss is not detected, laboratory testing is usually done to determine whether anemia is due to deficient RBC production or excessive hemolysis.

History

The history should address risk factors for particular anemias, symptoms of anemia itself, and symptoms that reflect the underlying disorder.

Anemia has many risk factors. For example, a vegan diet predisposes to vitamin B_{12} deficiency anemia, whereas alcoholism increases the risk of folate deficiency anemia. A number of hemoglobinopathies are inherited, and certain drugs predispose to hemolysis. Cancer, rheumatic disorders, and chronic inflammatory disorders can suppress bone marrow activity or enlarge the spleen.

The symptoms of anemia are neither sensitive nor specific and do not help differentiate between types of anemias. Symptoms reflect compensatory responses to tissue hypoxia and usually develop when Hb falls to < 7 g/dL. However, they may develop at higher Hb levels in patients with limited cardiopulmonary reserve or in whom the anemia developed very rapidly. Symptoms such as weakness, seeing spots, fatigue, drowsiness, angina, syncope, and dyspnea on exertion can indicate anemia. Vertigo, headache, pulsatile tinnitus, amenorrhea, loss of libido, and GI complaints may also occur. Heart failure or shock can develop in patients with severe tissue hypoxia or hypovolemia.

Certain symptoms may suggest the cause of the anemia. For example, melena, epistaxis, hematochezia, hematemesis, or menorrhagia indicates bleeding. Jaundice and dark urine, in the absence of liver disease, suggest hemolysis. Weight loss may suggest cancer. Diffuse severe bone or chest pain may suggest sickle cell disease, and stocking-glove paresthesias may suggest vitamin B_{12} or folate deficiency.

Physical Examination

Complete physical examination is necessary. Signs of anemia itself are neither sensitive nor specific; however, pallor is common with severe anemia.

Signs of underlying disorders are often more diagnostically accurate than are signs of anemia. Heme-positive stool identifies GI bleeding. Hemorrhagic shock (eg, hypotension, tachycardia, pallor, tachypnea, diaphoresis, confusion—see p. 2292) may result from acute bleeding. Jaundice may suggest hemolysis. Splenomegaly may occur with hemolysis, hemoglobinopathy, connective tissue disease, myeloproliferative disorder, infection, or cancer. Peripheral neuropathy suggests vitamin B_{12} deficiency. Abdominal distention in a patient with blunt trauma suggests acute hemorrhage. Petechiae develop in thrombocytopenia or platelet dysfunction. Fever and heart murmurs suggest infectious endocarditis, a possible cause of hemolysis. Rarely, high-output heart failure develops as a compensatory response to anemia-induced tissue hypoxia.

Testing

- CBC with WBC and platelets
- RBC indices and morphology

• Reticulocyte count

• Peripheral smear

• Sometimes bone marrow aspiration and biopsy

Laboratory evaluation begins with a CBC, including WBC and platelet counts, RBC indices and morphology (MCV, MCH, MCHC, RBC volume distribution width [RDW]), and examination of the peripheral smear. Reticulocyte count demonstrates how well the bone marrow compensates for the anemia. Subsequent tests are selected on the basis of these results and on the clinical presentation. Recognition of general diagnostic patterns can expedite the diagnosis (see Table 104-2).

The automated CBC directly measures Hb, RBC count, and MCV (a measure of RBC size). Hct (a measure of the percentage of blood made up of RBCs), MCH (a measure of the Hb content in individual RBCs), and MCHC (a measure of the Hb level in individual RBCs) are calculated values. The diagnostic criterion for anemia in men is Hb < 14 g/dL, Hct < 42%, or RBC < 4.5 million/L; for women, Hb < 12 g/dL, Hct < 37%, or RBC < 4 million/L. For infants, normal values vary with age, necessitating use of age-related tables. RBC populations are termed microcytic (small cells) if MCV is < 80 fL, and macrocytic (large cells) if MCV is > 100 fL. However, because reticulocytes are also larger than mature red cells, large numbers of reticulocytes can elevate the MCV and not represent an alteration of RBC production. Automated techniques can also determine the degree of variation in RBC size, expressed as the RDW. A high RDW may be the only indication of simultaneous microcytic and macrocytic disorders (or simultaneous microcytosis and reticulocytosis); such a pattern may result in a normal MCV, which measures only the mean value. The term hypochromia refers to RBC populations in which MCH is < 27 pg/RBC or MCHC is < 30%. RBC populations with normal MCH and MCHC values are normochromic.

The RBC indices can help indicate the mechanism of anemia and narrow the number of possible causes. Microcytic indices occur with altered heme or globin synthesis. The most common causes are iron deficiency, thalassemia, and related Hb-synthesis defects. In some patients with anemia of chronic disease, the MCV is microcytic or borderline microcytic. Macrocytic indices occur with impaired DNA synthesis (eg, due to vitamin B_{12} or folate deficiencies or chemotherapeutic drugs such as hydroxyurea and antifolate agents) and in alcoholism because of abnormalities of the cell membrane. Acute bleeding may briefly produce macrocytic indices because of the release of large young reticulocytes. Normocytic indices occur in anemias resulting from deficient EPO or inadequate response to it (hypoproliferative anemias). Hemorrhage, before iron deficiency develops, usually results in normocytic and normochromic anemia unless the number of large reticulocytes is excessive.

The peripheral smear is highly sensitive for excessive RBC production and hemolysis. It is more accurate than automated technologies for recognition of altered RBC structure, thrombocytopenia, nucleated RBCs, or immature granulocytes and can detect other abnormalities (eg, malaria and other parasites, intracellular RBC or granulocyte inclusions) that can occur despite normal automated blood cell counts. RBC injury may be identified by finding RBC fragments, portions of disrupted cells (schistocytes), or evidence of significant membrane alterations from oval-shaped cells (ovalocytes) or spherocytic cells. Target cells (thin RBCs with a central dot of Hb) are RBCs with insufficient Hb or excess cell membrane (eg, due to hemoglobinopathies or liver disorders). The peripheral smear can also reveal variation in RBC shape (poikilocytosis) and size (anisocytosis).

The reticulocyte count is expressed as the percentage of reticulocytes (normal range, 0.5 to 1.5%) or as the absolute reticulocyte count (normal range, 50,000 to 150,000/μL). Higher values indicate excessive production, or reticulocytosis; in the presence of anemia, reticulocytosis suggests excessive RBC destruction. Low numbers in the presence of anemia indicate decreased RBC production. The reticulocyte response can usually be estimated based on the number of blue-stained cells found when the peripheral smear is stained with a supravital stain; this estimates makes a reticulocyte count, which requires flow cytometry or a large amount of time, unnecessary.

Bone marrow aspiration and biopsy provide direct observation and assessment of RBC precursors.

The presence of abnormal maturation (dyspoiesis) of blood cells and the amount, distribution, and cellular pattern of iron content can be assessed. Bone marrow aspiration and biopsy are done to diagnose the following conditions:

• Unexplained anemias

• Other cytopenias

• Unexplained leukocytosis

[**Table 104-2.** Characteristics of Common Anemias]

• Thrombocytosis

• Suspected leukemia, multiple myeloma, or myelophthisis

Cytogenetic and molecular analyses can be done on aspirate material in hematopoietic or other tumors or in suspected congenital lesions of RBC precursors (eg, Fanconi's anemia). Flow cytometry can be done in suspected lymphoproliferative or myeloproliferative states to define the immunophenotype. Bone marrow aspiration and biopsy are not technically difficult and do not pose significant risk of morbidity. These procedures are safe and helpful when hematologic disease is suspected. Both usually can be done as a single procedure. Because biopsy requires adequate bone depth, the sample is usually taken from the posterior (or, less commonly, anterior) iliac crest. If only aspiration is necessary, the sternum may be used.

Serum bilirubin and LDH can sometimes help differentiate between hemolysis and blood loss; both are elevated in hemolysis and normal in blood loss. Other tests are discussed under specific anemias and bleeding disorders (see p. 921).

Treatment of Anemia

When possible, the cause of the anemia is treated. When the Hb falls dangerously low (eg, < 7 g/dL for patients without cardiopulmonary insufficiency or higher for patients with it), RBC transfusion temporarily increases O_2-carrying capacity. RBC transfusion should be reserved for patients

• With or at high risk of cardiopulmonary symptoms

• With active, uncontrollable blood loss

• With some form of hypoxic or ischemic end-organ failure (eg, neurologic ischemic symptoms, angina, tachycardia in patients with underlying heart failure or severe COPD)

Transfusion procedures and blood components are discussed in Ch. 121.

Chapter 105. Anemias Caused by Deficient Erythropoiesis

Introduction

Anemia (a decrease in the number of RBCs, Hb content, or Hct) can result from decreased RBC production (erythropoiesis), increased RBC destruction, or blood loss. Anemias due to decreased erythropoiesis are recognized by reticulocytopenia, which is usually evident on the peripheral smear (see p. 921). The RBC indices, mainly the MCV, narrow the differential diagnosis of deficient erythropoiesis and determine what further testing is necessary.

Microcytic anemias result from deficient or defective heme or globin synthesis. Microcytic anemias include iron deficiency anemias, iron-transport deficiency anemias, iron-utilization anemias (including some sideroblastic anemias and lead poisoning), and thalassemias (which also cause hemolysis—see p. 946). Patients with microcytic anemias typically require testing of iron stores (see below).

Normocytic anemias result from primary bone marrow failure. They are usually characterized by a normal RBC distribution width (RDW) and normochromic indices. The mechanisms involved are hypoproliferation (deficiency of or inadequate response to erythropoietin [EPO]), hypoplasia (in aplastic anemia), myelophthisis, and myelodysplasia.

Macrocytic anemias result most often from impaired DNA synthesis, as occurs with deficiencies of vitamin B_{12} or folate.

Some anemias have variable findings on the peripheral smear. Anemia of chronic disease may be microcytic or normocytic. Anemias due to myelodysplastic syndromes may be microcytic, normocytic, or macrocytic. Treatment of deficient RBC production depends on the cause; however, stimulation of erythropoiesis with human recombinant EPO often is helpful in the anemia due to renal failure. Because erythropoiesis increases the iron requirement, supplemental iron is helpful when administering any treatment that aims to increase erythropoiesis.

Iron Deficiency Anemia

(Anemia of Chronic Blood Loss; Chlorosis)

Iron deficiency is the most common cause of anemia and usually results from blood loss. Symptoms are usually nonspecific. RBCs tend to be microcytic and hypochromic, and iron stores are low as shown by low serum ferritin and low serum iron levels with high serum total iron binding capacity. If the diagnosis is made, occult blood loss is suspected. Treatment involves iron replacement and treatment of the cause of blood loss.

Pathophysiology

Iron is distributed in active metabolic and storage pools. Total body iron is about 3.5 g in healthy men and 2.5 g in women; the difference relates to women's smaller body size, lower androgen levels, and dearth of stored iron because of iron loss due to menses and pregnancy. The distribution of body iron in an average man is Hb, 2100 mg; ferritin, 700 mg (in cells and plasma); hemosiderin, 300 mg (in cells); myoglobin, 200 mg; tissue (heme and nonheme) enzymes, 150 mg; and transport-iron compartment, 3 mg.

Iron absorption: Iron is absorbed in the duodenum and upper jejunum. Absorption of iron is determined by the type of iron molecule and by what other substances are ingested. Iron absorption is best when food contains heme iron (meat). Dietary nonheme iron must be reduced to the ferrous state and released from food binders by gastric secretions. Nonheme iron absorption is reduced by other food items (eg, vegetable fiber phytates and polyphenols; tea tannates, including phosphoproteins; bran) and certain antibiotics (eg, tetracycline). Ascorbic acid is the only common food element known to increase nonheme iron absorption.

The average American diet, which contains 6 mg of elemental iron/kcal of food, is adequate for iron homeostasis. Of about 15 mg/day of dietary iron, adults absorb only 1 mg, which is the approximate amount lost daily by cell desquamation from the skin and intestines. In iron depletion, absorption increases, although the exact signaling mechanism is not known; however, absorption rarely increases to > 6 mg/day unless supplemental iron is added. Children have a greater need for iron and appear to absorb more to meet this need.

Iron transport and usage: Iron from intestinal mucosal cells is transferred to transferrin, an iron-transport protein synthesized in the liver; transferrin can transport iron from cells (intestinal, macrophages) to specific receptors on erythroblasts, placental cells, and liver cells. For heme synthesis, transferrin transports iron to the erythroblast mitochondria, which insert the iron into protoporphyrin for it to become heme. Transferrin (plasma half-life, 8 days) is extruded for reutilization. Synthesis of transferrin increases with iron deficiency but decreases with any type of chronic disease.

Iron storage and recycling: Iron not used for erythropoiesis is transferred by transferrin, an iron-transporting protein, to the storage pool; iron is stored in 2 forms, ferritin and hemosiderin. The most important is ferritin (a heterogeneous group of proteins surrounding an iron core), which is a soluble and active storage fraction located in the liver (in hepatocytes), bone marrow, and spleen (in macrophages); in RBCs; and in serum. Iron stored in ferritin is readily available for any body requirement. Circulating (serum) ferritin level parallels the size of the body stores (1 ng/mL = 8 mg of iron in the storage pool). The 2nd storage pool of iron is in hemosiderin, which is relatively insoluble and is stored primarily in the liver (in Kupffer cells) and in bone marrow (in macrophages).

Because iron absorption is so limited, the body recycles and conserves iron. Transferrin grasps and recycles available iron from aging RBCs undergoing phagocytosis by mononuclear phagocytes. This mechanism provides about 97% of the daily iron needed (about 25 mg of iron). With aging, iron stores tend to increase because iron elimination is slow.

Iron deficiency: Deficiency develops in stages. In the first stage, iron requirement exceeds intake, causing progressive depletion of bone marrow iron stores. As stores decrease, absorption of dietary iron increases in compensation. During later stages, deficiency impairs RBC synthesis, ultimately causing anemia.

Severe and prolonged iron deficiency also may cause dysfunction of iron-containing cellular enzymes.

Etiology

Because iron is poorly absorbed, dietary iron barely meets the daily requirement for most people. Even so, people who eat a typical Western diet are unlikely to become iron deficient solely as a result of dietary deficiency. However, even modest losses, increased requirements, or decreased intake readily causes iron deficiency.

Blood loss is almost always the cause. In men, the most frequent cause is chronic occult bleeding, usually from the GI tract. In premenopausal women, cumulative menstrual blood loss (mean, 0.5 mg iron/day) is a common cause. Another possible cause of blood loss in men and women is chronic intravascular hemolysis (see p. 934) when the amount of iron released during hemolysis exceeds the haptoglobin-binding capacity. Vitamin C deficiency can contribute to iron deficiency anemia by causing capillary fragility, hemolysis, and bleeding.

Increased iron requirement may contribute to iron deficiency. From birth to age 2 and during adolescence, when rapid growth requires a large iron intake, dietary iron often is inadequate. During pregnancy, the fetal iron requirement increases the maternal iron requirement (mean, 0.5 to 0.8 mg/day —see Anemia in Pregnancy on p. 2634) despite the absence of menses. Lactation also increases the iron requirement (mean, 0.4 mg/day).

Decreased iron absorption can result from gastrectomy and upper small-bowel malabsorption syndromes. Rarely, absorption is decreased by dietary deprivation from undernutrition.

Symptoms and Signs

Most symptoms of iron deficiency are due to anemia. Such symptoms include fatigue, loss of stamina, shortness of breath, weakness, dizziness, and pallor. Fatigue also may result from dysfunction of iron-containing cellular enzymes.

In addition to the usual manifestations of anemia, some uncommon symptoms occur in severe iron deficiency. Patients may have pica, an abnormal craving to eat substances (eg, ice, dirt, paint). Other symptoms of severe deficiency include glossitis, cheilosis, concave nails (koilonychia), and, rarely, dysphagia caused by a postcricoid esophageal web (Plummer-Vinson syndrome).

Diagnosis

• CBC, serum iron, iron-binding capacity, and serum ferritin

• Rarely bone marrow examination

Iron deficiency anemia is suspected in patients with chronic blood loss or microcytic anemia, particularly if pica is present. In such patients, CBC, serum iron and iron-binding capacity, and serum ferritin are obtained.

Iron and iron-binding capacity (or transferrin) are usually both measured because their relationship is important. Various tests exist; the range of normal values relates to the test used. In general, normal serum iron is 75 to 150 µg/dL (13 to 27 µmol/L) for men and 60 to 140 µg/dL (11 to 25 µmol/L) for women; total iron-binding capacity is 250 to 450 µg/dL (45 to 81 µmol/L). Serum iron level is low in iron deficiency and in many chronic diseases and is elevated in hemolytic disorders and in iron-overload syndromes (see p. 1032). Patients taking oral iron may have normal serum iron despite a deficiency; in such circumstances, a valid test requires cessation of iron therapy for 24 to 48 h. The iron-binding capacity increases in iron deficiency. Serum transferrin receptor levels reflect the amount of RBC precursors available for active proliferation; levels are sensitive and specific. The range of normal is 3.0 to 8.5 µg/mL. Levels increase in early iron deficiency and with increased erythropoiesis.

Serum ferritin levels closely correlate with total body iron stores. The range of normal in most laboratories is 30 to 300 ng/mL, and the mean is 88 ng/mL in men and 49 ng/mL in women. Low levels (< 12 ng/mL) are specific for iron deficiency. However, ferritin is an acute-phase reactant, and levels increase in inflammatory and neoplastic disorders, so ferritin may also be elevated in cases of liver injury (eg, hepatitis) and in some tumors (especially acute leukemia, Hodgkin lymphoma, and GI tract tumors).

The most sensitive and specific criterion for iron-deficient erythropoiesis is absent bone marrow stores of iron, although a bone marrow examination is rarely needed.

Stages of iron deficiency: Laboratory test results help stage iron deficiency anemia.

Stage 1 is characterized by decreased bone marrow iron stores; Hb and serum iron remain normal, but serum ferritin level falls to < 20 ng/mL. The compensatory increase in iron absorption causes an increase in iron-binding capacity (transferrin level).

During stage 2, erythropoiesis is impaired. Although the transferrin level is increased, the serum iron level decreases; transferrin saturation decreases. Erythropoiesis is impaired when serum iron falls to < 50 µg/dL (< 9 µmol/L) and transferrin saturation to < 16%. The serum ferritin receptor level rises (> 8.5 mg/L).

During stage 3, anemia with normal-appearing RBCs and indices develops.

During stage 4, microcytosis and then hypochromia develop.

During stage 5, iron deficiency affects tissues, resulting in symptoms and signs.

Diagnosis of iron deficiency anemia prompts consideration of its cause, usually bleeding. Patients with obvious blood loss (eg, women with menorrhagia) may require no further testing. Men and postmenopausal women without obvious blood loss should undergo evaluation of the GI tract, because anemia may be the only indication of an occult GI cancer. Rarely, chronic epistaxis or GU bleeding is underestimated by the patient and requires evaluation in patients with normal GI study results.

Other microcytic anemias: Iron deficiency anemia must be differentiated from other microcytic anemias (see Table 105-1). If tests exclude iron deficiency in patients with microcytic anemia, then anemia of chronic disease, structural Hb abnormalities (eg, hemoglobinopathies), and congenital RBC membrane abnormalities are considered. Clinical features, Hb studies (eg, Hb electrophoresis and Hb A_2), and genetic testing (eg, for α-thalassemia) may help distinguish these entities.

[**Table 105-1.** Differential Diagnosis of Microcytic Anemia Due to Decreased RBC Production]

Treatment

• Oral supplemental iron

• Rarely parenteral iron

Iron therapy without pursuit of the cause is poor practice; the bleeding site should be sought even in cases of mild anemia.

Iron can be provided by various iron salts (eg, ferrous sulfate, gluconate, fumarate) or saccharated iron po 30 min before meals (food or antacids may reduce absorption). A typical initial dose is 60 mg of elemental iron (eg, as 325 mg of ferrous sulfate) given once/day or bid. Larger doses are largely unabsorbed but increase adverse effects especially. Ascorbic acid either as a pill (500 mg) or as orange juice when taken with iron enhances iron absorption without increasing gastric distress. Parenteral iron causes the same therapeutic response as oral iron but can cause adverse effects, such as anaphylactoid reactions, serum sickness, thrombophlebitis, and pain. It is reserved for patients who do not tolerate or who will not take oral iron or for patients who steadily lose large amounts of blood because of capillary or vascular disorders (eg, hereditary hemorrhagic telangiectasia). The dose of parenteral iron is determined by a hematologist. Oral or parenteral iron therapy should continue for ≥ 6 mo after correction of Hb levels to replenish tissue stores.

The response to treatment is assessed by serial Hb measurements until normal RBC values are achieved. Hb rises little for 2 wk but then rises 0.7 to 1 g/wk until near normal, at which time rate of increase tapers. Anemia should be corrected within 2 mo. A subnormal response suggests continued hemorrhage, underlying infection or cancer, insufficient iron intake, or, very rarely, malabsorption of oral iron.

Sideroblastic Anemias

Sideroblastic anemias are iron-utilization anemias that are usually part of a myelodysplastic syndrome, causing a normocytic-normochromic anemia with high RBC distribution width or a microcytic-hypochromic anemia, particularly with increased serum iron and ferritin and transferrin saturation.

Sideroblastic anemias are among the anemias characterized by inadequate marrow utilization of iron for Hb synthesis despite the presence of adequate or increased amounts of iron (iron-utilization anemias). Other iron-utilization anemias include some hemoglobinopathies, primarily thalassemias (see p. 946). Sideroblastic anemias are characterized by the presence of polychromatophilic, stippled, targeted RBCs (siderocytes). Sideroblastic anemias are generally part of a myelodysplastic syndrome but may be hereditary or may occur secondary to drugs (eg, chloramphenicol, cycloserine, isoniazid, pyrazinamide) or toxins (including ethanol and lead). Pyridoxine deficiency can lead to sideroblastic anemia. Deficient reticulocyte production, intramedullary death of RBCs, and bone marrow erythroid hyperplasia (and dysplasia) occur. Although hypochromic RBCs are produced, other RBCs may be large, producing

normochromic indices; if so, variation in RBC size (dimorphism) usually produces a high RBC distribution width (RDW).

Sideroblastic anemia is suspected in patients with microcytic anemia or a high RDW anemia, particularly with increased serum iron, serum ferritin, and transferrin saturation (see Iron Deficiency Anemia on p. 924). The peripheral smear shows RBC dimorphism. RBCs may appear stippled. Bone marrow examination is necessary and reveals erythroid hyperplasia. Iron staining reveals the pathognomonic iron-engorged paranuclear mitochondria in developing RBCs (ringed sideroblasts). Other features of myelodysplasia, such as chromosomal abnormalities, are frequently evident. Serum lead is measured if sideroblastic anemia has an unknown cause.

Elimination of a toxin or drug (especially alcohol) can lead to recovery. Rarely, congenital cases respond to pyridoxine 50 mg po tid, but incompletely. Pyridoxine deficiency is corrected by vitamin B_6 supplementation.

Anemia of Chronic Disease

(Iron-Reutilization Anemia)

Anemia of chronic disease is a multifactorial anemia often coexistent with iron deficiency. Diagnosis generally requires the presence of chronic infection, inflammation, or cancer; microcytic or marginal normocytic anemia; and values for serum transferrin receptor and serum ferritin that are between those typical for iron deficiency and sideroblastic anemia. Treatment is to reverse the underlying disorder or, if the disorder is irreversible, to give erythropoietin.

Worldwide, anemia of chronic disease is the 2nd most common anemia. Early on, the RBCs are normocytic; with time they become microcytic. The major issue is that the marrow erythroid mass fails to expand appropriately in response to anemia.

Etiology

This type of anemia was thought to occur as part of a chronic disorder, most often infection, inflammatory disease (especially RA), or cancer; however, the same process appears to begin acutely during virtually any infection or inflammation. Three pathophysiologic mechanisms have been identified:

- Slightly shortened RBC survival occurs via unknown mechanisms in patients with cancer or chronic granulomatous infections.

- Erythropoiesis is impaired because of decreases in both erythropoietin (EPO) production and marrow responsiveness to EPO.

- Intracellular iron metabolism is impaired.

Reticuloendothelial cells retain iron from senescent RBCs, making iron unavailable for Hb synthesis. There is thus a failure to compensate for the anemia with increased RBC production. Macrophage-derived cytokines (eg, IL-1β, tumor necrosis factor-α, interferon-β) in patients with infections, inflammatory states, and cancer cause or contribute to the decrease in EPO production and the impaired iron metabolism.

Diagnosis

- Symptoms and signs of underlying disorder

- CBC and serum iron, ferritin, transferrin, and transferrin receptor

Clinical findings are usually those of the underlying disorder (infection, inflammation, or cancer). Anemia of chronic disease is suspected in patients with microcytic or marginal normocytic anemia with chronic infection, inflammation, or cancer. If anemia of chronic disease is suspected, serum iron, transferrin,

transferrin receptor, and serum ferritin are measured. Hb usually is > 8 g/dL unless an additional mechanism contributes to anemia (see also Table 105-1). If iron deficiency is present in addition to anemia of chronic disease, serum ferritin generally remains < 100 ng/mL, and, if there is infection, inflammation, or cancer, a ferritin level of slightly < 100 ng/mL suggests that iron deficiency is superimposed on anemia of chronic disease. However, because serum ferritin may be falsely elevated as an acute-phase reactant, the serum transferrin receptor measurement may better differentiate iron deficiency from anemia of chronic disease when serum ferritin is > 100 ng/mL.

Treatment

• Treatment of underlying disorder

• Recombinant EPO and iron supplements

Treating the underlying disorder is most important. Because the anemia is generally mild, transfusions usually are not required, and recombinant EPO may be offered. Because both reduced production of and marrow resistance to EPO occur, the EPO dose may need to be 150 to 300 units/kg sc 3 times/wk. A good response is likely if after 2 wk of therapy Hb has increased > 0.5 g/dL and serum ferritin is < 400 ng/mL. Iron supplements (see p. 927) are required to ensure an adequate response to EPO. However, careful monitoring of Hb response is needed because adverse effects (eg, venous thromboembolism, MI, death) may occur when Hb rises to > 12 g/dL.

Hypoproliferative Anemias

Hypoproliferative anemias result from deficient erythropoietin (EPO) or a diminished response to it; they tend to be normocytic and normochromic. Renal, metabolic, and endocrine disorders are common causes. Treatment includes measures to correct the underlying disorder and sometimes EPO.

Hypoproliferation is a common mechanism in anemias of renal disease, hypometabolic or endocrine deficiency states (eg, hypothyroidism, hypopituitarism), and protein deprivation. The mechanism appears to be a relative or absolute decreased production of EPO. In hypometabolic states, the bone marrow may also fail to respond to EPO.

Anemia of renal disease: The deficiency in renal production of EPO and the severity of anemia correlate with the extent of renal dysfunction; anemia occurs when creatinine clearance is < 45 mL/min. Renal glomerular lesions (eg, from amyloidosis, diabetic nephropathy) generally result in the most severe anemia for their degree of excretory failure.

The term anemia of renal disease refers only to that caused by decreased EPO, but other mechanisms may increase its severity. In uremia, mild hemolysis is common; its basis is uncertain. Less common is RBC fragmentation (traumatic hemolytic anemia), which occurs when the renovascular endothelium is injured (eg, in malignant hypertension, membranoproliferative glomerulonephritis, polyarteritis nodosa, or acute cortical necrosis). Traumatic hemolysis in children can be an acute, sometimes fatal illness called hemolytic-uremic syndrome (see p. 961).

Diagnosis is based on demonstration of renal insufficiency and normocytic anemia, peripheral reticulocytopenia, and a paucity of erythroid hyperplasia for the degree of anemia. RBC fragmentation on the peripheral smear, particularly if there is thrombocytopenia, suggests simultaneous traumatic hemolysis.

Therapy is directed at improving renal function and increasing RBC production. If renal function returns to normal, anemia is slowly corrected. In patients receiving long-term dialysis, EPO, beginning with 50 to 100 units/kg IV or sc 3 times/wk with iron supplements, is the treatment of choice. In almost all cases, maximum increases in RBCs are reached by 8 to 12 wk. Reduced doses of EPO (about one half the induction dose) can then be given 1 to 3 times/wk. Transfusions are rarely necessary. Careful monitoring of the response is needed to avoid adverse effects when Hb increases to > 12 g/dL.

Other hypoproliferative anemias: Clinical and laboratory findings of other hypoproliferative normochromic-normocytic anemias are milder but otherwise mimic those of the anemia of renal disease. The mechanism of the anemia of protein depletion may be general hypometabolism. Hypometabolism may diminish the marrow response to EPO. Protein's role in hematopoiesis is unclear.

Aplastic Anemia

(Hypoplastic Anemia)

Aplastic anemia is a normocytic-normochromic anemia that results from a loss of blood cell precursors, causing hypoplasia of bone marrow, RBCs, WBCs, and platelets. Symptoms result from severe anemia, thrombocytopenia (petechiae, bleeding), or leukopenia (infections). Diagnosis requires demonstration of peripheral pancytopenia and the absence of cell precursors in bone marrow. Treatment is equine antithymocyte globulin and cyclosporine. Erythropoietin, granulocyte-macrophage colony-stimulating factor, and bone marrow transplantation may also be useful.

The term aplastic anemia commonly implies a panhypoplasia of the marrow with associated leukopenia and thrombocytopenia. In contrast, pure RBC aplasia is restricted to the erythroid cell line. Although both disorders are uncommon, aplastic anemia is more common.

Etiology

True aplastic anemia (most common in adolescents and young adults) is idiopathic in about one half of cases. Recognized causes are chemicals (eg, benzene, inorganic arsenic), radiation, and drugs (eg, antineoplastic drugs, antibiotics, NSAIDs, anticonvulsants, acetazolamide, gold salts, penicillamine, quinacrine). The mechanism is unknown, but selective (perhaps genetic) hypersensitivity appears to be the basis.

Fanconi's anemia is a very rare, familial form of aplastic anemia with bone abnormalities, microcephaly, hypogonadism, and brown pigmentation of skin. It occurs in children with abnormal chromosomes. Fanconi's anemia is often inapparent until some illness (especially an acute infection or inflammatory disorder) supervenes, causing peripheral cytopenias. With clearing of the supervening illness, peripheral values return to normal despite reduced marrow mass.

Pure RBC aplasia may be acute and reversible. Acute erythroblastopenia is a brief disappearance of RBC precursors from the bone marrow during various acute viral illnesses (particularly human parvovirus infection), especially in children. The anemia lasts longer than the acute infection. Chronic pure RBC aplasia has been associated with hemolytic disorders, thymomas, and autoimmune mechanisms and, less often, with drugs (eg, tranquilizers, anticonvulsants), toxins (organic phosphates), riboflavin deficiency, and chronic lymphocytic leukemia. A rare congenital form, Diamond-Blackfan anemia, usually occurs during infancy but has also been reported in adulthood. Diamond-Blackfan anemia is associated with bony abnormalities of the thumbs or digits and short stature.

Symptoms and Signs

Although onset of aplastic anemia usually is insidious, often occurring over weeks or months after exposure to a toxin, occasionally it is acute. Signs vary with the severity of the pancytopenia. Symptoms and signs of anemia (eg, pallor) usually are severe.

Severe thrombocytopenia may cause petechiae, ecchymosis, and bleeding from the gums, into the conjunctivae, or other tissues. Agranulocytosis commonly causes life-threatening infections. Splenomegaly is absent unless induced by transfusion hemosiderosis. Symptoms of pure RBC aplasia are generally milder and relate to the degree of the anemia or to the underlying disorder.

Diagnosis

• CBC

• Bone marrow examination

Aplastic anemia is suspected in patients, particularly young patients, with pancytopenia (eg, WBC < 1500/µL, platelets < 50,000/µL). Pure RBC aplasia (including Diamond-Blackfan anemia) is suspected in patients with bony abnormalities and normocytic anemia but normal WBC and platelet counts. If either diagnosis is suspected, bone marrow examination is done.

In aplastic anemia, RBCs are normochromicnormocytic (sometimes marginally macrocytic). The WBC count reduction occurs chiefly in the granulocytes. Platelets are often far below 50,000/µL. Reticulocytes are decreased or absent. Serum iron is elevated. The bone marrow is acellular. In pure RBC aplasia, normocytic anemia, reticulocytopenia, and elevated serum iron are present, but WBC and platelet counts are normal. Bone marrow cellularity and maturation may be normal except for absence of erythroid precursors.

Treatment

• Equine antithymocyte globulin, corticosteroids, and cyclosporine

• Sometimes hematopoietic cell transplantation

• Sometimes cytokines

• Sometimes surgery in thymoma-associated RBC aplasia

In aplastic anemia, treatment of choice is equine antithymocyte globulin (ATG) 10 to 20 mg/kg diluted in 500 mL saline and infused IV over 4 to 6 h once/day for 10 consecutive days. Shorter regimens are also used. About 60% of patients respond to ATG. Allergic reactions and serum sickness may occur; some experts advocate skin testing (to identify allergy to horse serum) and concomitant corticosteroids (prednisone 40 mg/m^2 po once/day beginning on day 7 for 10 days or until symptoms subside). Cyclosporine (5 to 10 mg/kg po once/day) is as effective as ATG and produces responses in about 50% of patients who do not respond to ATG, suggesting that its mechanism of action is different. Combined ATG and cyclosporine is also effective. If aplastic anemia is very severe or fails to respond to ATG and cyclosporine, bone marrow transplantation or treatment with cytokines (erythropoietin, granulocyte colony-stimulating factor, or granulocyte-macrophage colony-stimulating factor) may be effective.

Hematopoietic stem cell transplantation may help younger patients (particularly patients < 30) but requires an identical twin or an HLA-compatible sibling. At diagnosis, siblings are evaluated for HLA compatibility. Because transfusions pose a risk to subsequent transplantation, blood products are used only when essential.

Pure RBC aplasia has been successfully managed with immunosuppressants (prednisone, cyclosporine, or cyclophosphamide), especially when an autoimmune mechanism is suspected. Because patients with thymoma-associated pure RBC aplasia improve after thymectomy, CT is used to seek the presence of such a lesion, and surgery is considered.

Myelophthisic Anemia

Myelophthisic anemia is a normocytic-normochromic anemia that occurs when normal marrow space is infiltrated and replaced by nonhematopoietic or abnormal cells. Causes include tumors, granulomatous disorders, and lipid storage diseases. Marrow fibrosis often occurs. Splenomegaly may develop. Characteristic changes in peripheral blood include anisocytosis, poikilocytosis, and excessive numbers of RBC and WBC precursors. Diagnosis usually requires bone marrow biopsy. Treatment is supportive and includes measures directed at the underlying disorder.

Descriptive terms used in this anemia can be confusing. Myelofibrosis, which is replacement of marrow by fibrous tissue bands, may be idiopathic (primary) or secondary. True myelofibrosis is a stem cell defect

in which the fibrosis is secondary to other hematopoietic intramedullary events. Myelosclerosis is new bone formation that sometimes accompanies myelofibrosis. Myeloid metaplasia refers to extramedullary hematopoiesis in the liver, spleen, or lymph nodes that may accompany myelophthisis due to any cause. An old term, agnogenic myeloid metaplasia, indicates primary myelofibrosis with or without myeloid metaplasia.

Etiology

The most common cause is replacement of bone marrow by metastatic cancer (most often, breast or prostate; less often, kidney, lung, adrenal, or thyroid); extramedullary hematopoiesis tends to be modest. Other causes include myeloproliferative disorders (especially late-stage or spent polycythemia vera), granulomatous diseases, and (lipid) storage diseases. Myelofibrosis can occur in all of these.

Factors that may contribute to decreased RBC production include a decreased amount of functioning hematopoietic tissue, disordered metabolism related to the underlying disorder, and, in some cases, erythrophagocytosis. Extramedullary hematopoiesis or disruption of the marrow sinusoids causes release of immature cells. Abnormally shaped RBCs often result in increased RBC destruction.

Symptoms and Signs

Myeloid metaplasia may result in splenomegaly, particularly in patients with storage diseases. In severe cases, symptoms of anemia and of the underlying disorder may be present. Massive splenomegaly can cause abdominal pressure, early satiety, and left upper quadrant abdominal pain; hepatomegaly may be present. Hepatosplenomegaly is rare with myelofibrosis from malignant tumors.

Diagnosis

• CBC, RBC indices, reticulocyte count, and peripheral smear

• Bone marrow examination

Myelophthisic anemia is suspected in patients with normocytic anemia, particularly when splenomegaly or a potential underlying disorder is present. If it is suspected, a peripheral smear should be obtained, because a leukoerythroblastic pattern (immature myeloid cells and nucleated RBCs, such as normoblasts in the smear) suggests myelophthisic anemia. Anemia, usually moderately severe, is characteristically normocytic but may be slightly macrocytic. RBC morphology may show extreme variation (anisocytosis and poikilocytosis) in size and shape. The WBC count may vary. The platelet count is often low, and platelets are often large and bizarre in shape. Reticulocytosis often occurs; it may be caused by premature release of reticulocytes from the marrow or extramedullary sites and thus does not always indicate increased blood regeneration.

Although examination of peripheral blood can be suggestive, diagnosis usually requires bone marrow examination. Indications include a leukoerythroblastic pattern and unexplained splenomegaly. The marrow may be difficult to aspirate; marrow trephine biopsy is usually required. Findings vary according to the underlying disorder. Erythropoiesis is normal or increased in some cases. However, the life span of RBCs is often reduced. Hematopoiesis may be present in the spleen and liver.

X-rays, if obtained incidentally, may disclose bony lesions (myelosclerosis) characteristic of long-standing myelofibrosis or other osseous changes (ie, osteoblastic or lytic lesions of a tumor), suggesting the cause of anemia.

Treatment

• Treatment of underlying disorder

• Transfusions and corticosteroids

• Hydroxyurea

• Possibly thalidomide

The underlying disorder is treated. In idiopathic cases, management is supportive. Erythropoietin (20,000 to 40,000 units sc once/wk or twice/wk) and corticosteroids (eg, prednisone 10 to 30 mg po once/day) have been used, but only modest responses have been observed. Hydroxyurea (500 mg po once/day or once every other day) decreases spleen size and normalizes RBC values in many patients, but the response requires 6 to 12 mo of treatment. Thalidomide (50 to 100 mg po once/day in the evening) may provide modest responses, but it increases the risk of thrombosis and causes fatigue, which can be severe.

Megaloblastic Macrocytic Anemias

Megaloblastic anemias result most often from deficiencies of vitamin B_{12} and folate. Ineffective hematopoiesis affects all cell lines but particularly RBCs. Diagnosis is usually based on a CBC and peripheral smear, which may show a macrocytic anemia with anisocytosis and poikilocytosis, large oval RBCs (macro-ovalocytes), hypersegmented neutrophils, and reticulocytopenia. Treatment is directed at the underlying disorder.

Macrocytes are enlarged RBCs (ie, MCV > 100 fL/cell). Macrocytic RBCs occur in a variety of clinical circumstances, many unrelated to the megaloblastosis and the resultant anemia. Macrocytosis may be due to megaloblasts or other enlarged RBCs (see Sidebar 105-1). Megaloblasts are large nucleated RBC precursors with noncondensed chromatin. Megaloblastosis precedes macrocytic anemia.

Etiology

The most common cause of megaloblastic states is deficiency or defective utilization of vitamin B_{12} (see p. 37) or folate (see p. 29). Other causes include drugs (generally antineoplastics or immunosuppressants) that interfere with DNA synthesis and rare metabolic disorders (eg, hereditary orotic aciduria); some cases are of unknown etiology.

Pathophysiology

Megaloblastic states result from defective DNA synthesis. RNA synthesis continues, resulting in a large cell with a large nucleus. All cell lines have dyspoiesis, in which cytoplasmic maturity is greater than nuclear maturity; this dyspoiesis produces megaloblasts in the marrow before they appear in the peripheral blood. Dyspoiesis results in intramedullary cell death, making erythropoiesis ineffective and causing indirect hyperbilirubinemia and hyperuricemia. Because dyspoiesis affects all cell lines, reticulocytopenia and, during later stages, leukopenia and thrombocytopenia develop. Large, oval RBCs (macro-ovalocytes) enter the circulation. Hypersegmentation of polymorphonuclear neutrophils is common; the mechanism of their production is unknown.

Symptoms and Signs

Anemia develops insidiously and may not cause symptoms until it is severe. Deficiencies of vitamin B_{12} may cause neurologic manifestations, including peripheral neuropathy, dementia, and subacute combined degeneration. Folate deficiency may also cause diarrhea and glossitis. Many patients with folate deficiency appear wasted, particularly with temporal wasting.

Diagnosis

• CBC, RBC indices, reticulocyte count, and peripheral smear

• Sometimes bone marrow examination

Megaloblastic anemia is suspected in anemic patients with macrocytic indices. Diagnosis is usually based on peripheral smear. When fully developed, the anemia is macrocytic, with MCV > 100 fL/cell. The smear

shows macro-ovalocytosis, anisocytosis, and poikilocytosis. The RBC distribution width (RDW) is high. Howell-Jolly bodies (residual fragments of the nucleus) are common. Reticulocytopenia is present. Hypersegmentation of the granulocytes develops early; neutropenia develops later. Thrombocytopenia is often present in severe cases, and platelets may be bizarre in size and shape. If the diagnosis is questionable, a bone marrow examination may be needed.

Treatment

Before treatment, the cause must be identified. Deficiency of vitamin B_{12} or folate is suspected if megaloblastic anemia is recognized; these disorders are indistinguishable on the basis of peripheral blood and bone marrow findings, so vitamin B_{12} and folate levels are required (see pp. 30 and 39).

Sidebar 105-1 Nonmegaloblastic Macrocytosis

Most macrocytic (ie, MCV > 100 fL/cell) anemias are megaloblastic. Nonmegaloblastic macrocytosis occurs in various clinical states, not all of which are understood. Anemia commonly occurs in patients with macrocytosis but usually results from mechanisms independent of macrocytosis.

Macrocytosis due to excess RBC membrane occurs in patients with chronic liver disease when cholesterol esterification is defective. Macrocytosis with an MCV of about 100 to 105 fL/cell can occur with chronic alcohol use in the absence of folate deficiency. Mild macrocytosis can occur in aplastic anemia, especially as recovery occurs. Macrocytosis is also common in myelodysplasia. Because RBC membrane molding occurs in the spleen after cell release from the marrow, RBCs may be slightly macrocytic after splenectomy, although these changes are not associated with anemia.

Nonmegaloblastic macrocytosis is suspected in patients with macrocytic anemias when testing excludes vitamin B_{12} and folate deficiencies. The macro-ovalocytes on peripheral smear and the increased RBC distribution width that are typical of classic megaloblastic anemia may be absent. If nonmegaloblastic macrocytosis is unexplained clinically (eg, by the presence of aplastic anemia, chronic liver disease, or alcohol use) or if myelodysplasia is suspected, bone marrow examination and cytogenetic analysis are done to exclude myelodysplasia. In nonmegaloblastic macrocytosis, the marrow is not megaloblastic, but in myelodysplasia and advanced liver disease there are megaloblastoid RBC precursors with dense nuclear chromatin that differ from the usual fine fibrillar pattern in megaloblastic anemias.

Treatment depends on the cause. For treatment of folate and vitamin B_{12} deficiencies, see pp. 30 and 39. Drugs causing megaloblastic states may need to be eliminated or given in reduced doses.

Myelodysplasia and Iron-Transport Deficiency Anemia

In myelodysplastic syndrome (see p. 1014), anemia is commonly prominent. The anemia can be microcytic or normochromic-normocytic, usually with a dimorphic (large and small) population of circulating cells. Bone marrow examination shows decreased erythroid activity, megaloblastoid and dysplastic changes, and, sometimes, increased numbers of ringed sideroblasts. Treatment is the same as for sideroblastic anemias (see p. 928).

Iron-transport deficiency anemia (atransferrinemia) is exceedingly rare. It occurs when iron cannot move from storage sites (eg, mucosal cells, liver) to the erythropoietic precursors. The presumed mechanism is absence of transferrin or presence of a defective transferrin molecule. In addition to anemia, hemosiderosis of lymphoid tissue, especially along the GI tract, is prominent.

Chapter 106. Anemias Caused by Hemolysis

Introduction

At the end of their normal life span (about 120 days), RBCs are removed from the circulation. Hemolysis involves premature destruction and hence a shortened RBC life span (< 120 days). Anemia results when bone marrow production can no longer compensate for the shortened RBC survival; this condition is termed hemolytic anemia. If the marrow can compensate, the condition is termed compensated hemolytic anemia.

Etiology

Hemolysis can result from disorders extrinsic to the RBC or from intrinsic RBC abnormalities (see Table 106-1).

Disorders extrinsic to the RBC: Most extrinsic disorders are acquired; the RBCs are normal and transfused cells as well as autologous cells are destroyed. Disorders extrinsic to the RBC include reticuloendothelial hyperactivity (hypersplenism—see p. 985), immunologic abnormalities (eg, autoimmune hemolytic anemia, isoimmune hemolytic anemia), mechanical injury (traumatic hemolytic anemia), and certain infections. Infectious organisms may cause hemolytic anemia through the direct action of toxins (eg, from *Clostridium perfringens*, α- or β-hemolytic streptococci, meningococci) or by invasion and destruction of RBC by the organism (eg, *Plasmodium* sp, *Bartonella* sp).

Intrinsic RBC abnormalities: Defects intrinsic to the RBC that can cause hemolysis involve one or more components or functions of the RBC: the membrane, cell metabolism, and the Hb. Abnormalities include hereditary and acquired cell membrane disorders (eg, spherocytosis), disorders of RBC metabolism (eg, G6PD deficiency), and hemoglobinopathies (eg, sickle cell diseases, thalassemias). Quantitative and functional abnormalities of certain RBC membrane proteins (α- and β-spectrin, protein 4.1, F-actin, ankyrin) cause hemolytic anemias.

Pathophysiology

Hemolysis may be acute, chronic, or episodic. Chronic hemolysis may be complicated by aplastic crisis (temporary failure of erythropoiesis), usually caused by an infection, often parvovirus. Hemolysis can be extravascular, intravascular, or both.

[**Table 106-1.** Hemolytic Anemias]

Normal RBC processing: Senescent RBCs lose membrane and are cleared from the circulation largely by the phagocytic cells of the spleen, liver, bone marrow, and reticuloendothelial system. Hb is broken down in these cells primarily by the heme oxygenase system. The iron is conserved and reutilized, and heme is degraded to bilirubin, which is conjugated in the liver to bilirubin glucuronide and excreted in the bile.

Extravascular hemolysis: Most pathologic hemolysis is extravascular and occurs when damaged or abnormal RBCs are cleared from the circulation by cells of the spleen, liver, and bone marrow similar to the process by which senescent RBCs are removed. The spleen usually contributes to hemolysis by destroying mildly abnormal RBCs or cells coated with warm antibodies. An enlarged spleen may sequester even normal RBCs. Severely abnormal RBCs or RBCs coated with cold antibodies or complement (C3) are destroyed within the circulation and in the liver, which (because of its large blood flow) can remove damaged cells efficiently.

Intravascular hemolysis: Intravascular hemolysis is an important reason for premature RBC destruction and usually occurs when the cell membrane has been severely damaged by any of a number of different mechanisms, including autoimmune phenomena, direct trauma (eg, march hemoglobinuria), shear stress (eg, defective mechanical heart valves), and toxins (eg, clostridial toxins, venomous snake bite).

Intravascular hemolysis results in hemoglobinemia when the amount of Hb released into plasma exceeds the Hb-binding capacity of the plasma-binding protein haptoglobin, a globulin normally present in concentrations of about 1.0 g/L in plasma. With hemoglobinemia, unbound Hb dimers are filtered into the urine and reabsorbed by renal tubular cells; hemoglobinuria results when reabsorptive capacity is exceeded. Iron is embedded in hemosiderin within the tubular cells; some of the iron is assimilated for reutilization and some reaches the urine when the tubular cells slough.

Consequences of hemolysis: Unconjugated (indirect) hyperbilirubinemia and jaundice occur when the conversion of Hb to bilirubin exceeds the liver's capacity to conjugate and excrete bilirubin (see p. 270). Bilirubin catabolism causes increased stercobilin in the stool and urobilinogen in the urine and sometimes cholelithiasis.

The bone marrow responds to the excess loss of RBCs by accelerating production and release of RBCs, resulting in a reticulocytosis.

Symptoms and Signs

Systemic manifestations resemble those of other anemias and include pallor, fatigue, dizziness, and possible hypotension. Hemolytic crisis (acute, severe hemolysis) is uncommon; it may be accompanied by chills, fever, pain in the back and abdomen, prostration, and shock. Severe hemolysis can cause jaundice and splenomegaly. Hemoglobinuria causes red or reddish-brown urine.

Diagnosis

• Peripheral smear, reticulocyte count, serum bilirubin, LDH, and ALT

• Sometimes, measurement of urinary hemosiderin and serum haptoglobin

• Rarely, measurement of RBC survival using a radioactive label

Hemolysis is suspected in patients with anemia and reticulocytosis, particularly if splenomegaly or another possible cause is recognized. If hemolysis is suspected, peripheral smear is examined and serum bilirubin, LDH, and ALT are measured. If results of these tests are inconclusive, urinary hemosiderin and serum haptoglobin are measured.

Abnormalities of RBC morphology are seldom diagnostic but often suggest the presence and cause of hemolysis (see
Table 106-2).

[**Table 106-2.** RBC Morphologic Changes in Hemolytic Anemias]

Other suggestive findings include increased levels of serum LDH and indirect bilirubin with a normal ALT, and the presence of urinary urobilinogen. Intravascular hemolysis is suggested by RBC fragments (schistocytes) on the peripheral smear and by decreased serum haptoglobin levels; however, haptoglobin levels can decrease because of hepatocellular dysfunction and can increase because of systemic inflammation. Intravascular hemolysis is also suggested by urinary hemosiderin. Urinary Hb, like hematuria and myoglobinuria, produces a positive benzidine reaction on dipstick testing; it can be differentiated from hematuria by the absence of RBCs on microscopic urine examination. Free Hb may make plasma reddish brown, noticeable often in centrifuged blood; myoglobin does not.

Although hemolysis can usually be identified by these simple criteria, the definitive diagnosis is demonstration of decreased RBC survival, preferably with a radioactive label, such as radiochromium (^{51}Cr). The measured survival of radiolabeled RBCs can establish hemolysis and also identify the sites of sequestration by using body surface counting. This procedure is rarely required, however.

Once hemolysis has been identified, the specific disorder is sought. One approach to narrowing the differential diagnosis in hemolytic anemias is to consider risk factors (eg, geographic location, genetics, underlying disorder), examine the patient for splenomegaly, and do a direct antiglobulin (Coombs') test

and peripheral smear; most hemolytic anemias produce abnormalities in one of these variables that can direct further testing. Other laboratory tests that can help discern the causes of hemolysis include the following:

• Quantitative Hb electrophoresis

• RBC enzyme assays

• Flow cytometry

• Cold agglutinins

• Osmotic fragility

Although some tests can help differentiate intravascular from extravascular hemolysis, making the distinction is sometimes difficult. During increased RBC destruction, both types are commonly involved, although to differing degrees.

Treatment

Treatment depends on the specific mechanism of hemolysis.

Hemoglobinuria and hemosiderinuria may necessitate iron-replacement therapy. Corticosteroids are helpful in the initial treatment of warm antibody autoimmune hemolysis. Long-term transfusion therapy may cause excessive iron accumulation, necessitating chelation therapy. Splenectomy is beneficial in some situations, particularly when splenic sequestration is the major cause of RBC destruction. If possible, splenectomy is delayed until 2 wk after vaccination with pneumococcal, *Haemophilus influenzae*, and meningococcal vaccines. In cold agglutinin disease, the patient is kept warm. Folate replacement is needed for patients with ongoing long-term hemolysis.

Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia is caused by autoantibodies that react with RBCs at temperatures ≥ 37° C (warm antibody hemolytic anemia) or < 37° C (cold agglutinin disease). Hemolysis is usually extravascular. The direct antiglobulin (Coombs') test establishes the diagnosis and may suggest the cause. Treatment depends on the cause and may include corticosteroids, splenectomy, IV immune globulin, immunosuppressants, avoidance of blood transfusions, and withdrawal of drugs.

Etiology

Warm antibody hemolytic anemia: Warm antibody hemolytic anemia is the most common form of autoimmune hemolytic anemia (AIHA); it is more common among women. Autoantibodies in warm antibody hemolytic anemia generally react at temperatures ≥ 37° C. They may occur spontaneously or in association with certain disorders (SLE, lymphoma, chronic lymphocytic leukemia). Some drugs (eg, α-methyldopa, levodopa—see Table 106-3) stimulate production of autoantibodies against Rh antigens (α-methyldopa-type of AIHA). Other drugs stimulate production of autoantibodies against the antibiotic-RBC-membrane complex as part of a transient hapten mechanism; the hapten may be stable (eg, high-dose penicillin, cephalosporins) or unstable (eg, quinidine, sulfonamides).

In warm antibody hemolytic anemia, hemolysis occurs primarily in the spleen. It is often severe and can be fatal. Most of the autoantibodies in warm antibody hemolytic anemia are IgG. Most are panagglutinins and have limited specificity.

Cold agglutinin disease: Cold agglutinin disease (cold antibody disease) is caused by autoantibodies that react at temperatures < 37° C. It sometimes occurs with infections

[Table 106-3. Drugs that Cause Warm Antibody Hemolytic Anemia]

(especially mycoplasmal pneumonias or infectious mononucleosis) and lymphoproliferative states; about one half of cases are idiopathic, which is the common form in older adults. Infections tend to cause acute disease, whereas idiopathic disease tends to be chronic. The hemolysis occurs largely in the extravascular mononuclear phagocyte system of the liver. The anemia is usually mild (Hb > 7.5 g/dL). Autoantibodies in cold agglutinin disease are usually IgM. The higher the temperature (ie, the closer to normal body temperature) at which these antibodies react with the RBC, the greater the hemolysis.

Paroxysmal cold hemoglobinuria: Paroxysmal cold hemoglobinuria (PCH; Donath-Landsteiner syndrome) is a rare type of cold agglutinin disease. Hemolysis results from exposure to cold, which may even be localized (eg, from drinking cold water, from washing hands in cold water). An IgG autohemolysin binds to RBCs at low temperatures and causes intravascular hemolysis after warming. It occurs most often after a nonspecific viral illness or in otherwise healthy patients, although it occurs in some patients with congenital or acquired syphilis. The severity and rapidity of development of the anemia varies and may be fulminant.

Symptoms and Signs

Symptoms of warm antibody hemolytic anemia tend to be due to the anemia. If the disorder is severe, fever, chest pain, syncope, or heart failure may occur. Mild splenomegaly is typical.

Cold agglutinin disease manifests as an acute or chronic hemolytic anemia. Other cryopathic symptoms or signs may be present (eg, acrocyanoses, Raynaud's syndrome, cold-associated occlusive changes). Symptoms of PCH may include severe pain in the back and legs, headache, vomiting, diarrhea, and passage of dark brown urine; hepatosplenomegaly may be present.

Diagnosis

- Assays for hemolytic anemia (eg, peripheral smear, reticulocyte count; sometimes urinary hemosiderin, serum haptoglobin)

- Direct antiglobulin test

AIHA is suspected in patients with hemolytic anemia, particularly if symptoms are severe or other suggestive symptoms are present. Routine laboratory tests generally suggest extravascular hemolysis (eg, hemosiderinuria is absent; haptoglobin levels are near normal) unless anemia is sudden and severe or PCH is the cause. Spherocytosis and a high MCHC are typical.

AIHA is diagnosed by detection of autoantibodies with the direct antiglobulin (direct Coombs') test. Antiglobulin serum is added to washed RBCs from the patient; agglutination indicates the presence of immunoglobulin or complement (C) bound to the RBCs. Generally IgG is present in warm antibody hemolytic anemia, and C3 (C3b and C3d) in cold antibody disease. The test is ≤ 98% sensitive for AIHA; false-negative results can occur if antibody density is very low or if the autoantibodies are IgA or IgM. In general, the intensity of the direct antiglobulin test correlates with the number of molecules of IgG or C3 bound to the RBC and, roughly, with the rate of hemolysis. A complementary test consists of mixing the patient's plasma with normal RBCs to determine whether such antibodies are free in the plasma (the indirect antiglobulin [indirect Coombs'] test). A positive indirect antiglobulin test and a negative direct test generally indicate an alloantibody caused by pregnancy, prior transfusions, or lectin cross-reactivity rather than immune hemolysis. Even identification of a warm antibody does not define hemolysis, because 1/10,000 healthy blood donors has a positive test result.

Once AIHA has been identified by the Coombs' test, testing should differentiate between warm antibody hemolytic anemia and cold agglutinin disease as well as the mechanism responsible for warm antibody hemolytic anemia. This determination can often be made by observing the pattern of the direct antiglobulin reaction. Three patterns are possible:

- The reaction is positive with anti-IgG and negative with anti-C3. This pattern is common in idiopathic

AIHA and in the drug-associated or α-methyldopa-type of AIHA, usually warm antibody hemolytic anemia.

- The reaction is positive with anti-IgG and anti-C3. This pattern is common in patients with SLE and idiopathic AIHA, usually warm antibody hemolytic anemia, and is rare in drug-associated cases.

- The reaction is positive with anti-C3 but negative with anti-IgG. This pattern occurs in cold agglutinin disease. It is uncommon in idiopathic AIHA, warm antibody hemolytic anemia, when the IgG antibody is of low affinity, in some drug-associated cases, and in PCH.

Other studies can suggest the cause of AIHA but are not definitive. In cold agglutinin disease, RBCs clump on the peripheral smear, and automated cell counts often reveal an increased MCV and spuriously low Hb due to such clumping; hand warming of the tube and recounting result in values significantly closer to normal. Warm antibody hemolytic anemia can often be differentiated from cold agglutinin disease by the temperature at which the direct antiglobulin test is positive; a test that is positive at temperatures ≥ 37° C indicates warm antibody hemolytic anemia, whereas a test that is positive at lower temperatures indicates cold agglutinin disease.

If PCH is suspected, the Donath-Landsteiner test, which is specific for PCH, should be done. Testing for syphilis is recommended.

Treatment

- For drug-induced warm antibody hemolytic anemia, drug withdrawal, sometimes IV immune globulin

- For idiopathic warm antibody hemolytic anemia, corticosteroids

- For cold agglutinin disease, avoidance of cold

Treatment depends on the specific mechanism of the hemolysis.

Warm antibody hemolytic anemias: In drug-induced warm antibody hemolytic anemias, drug withdrawal decreases the rate of hemolysis. With α-methyldopa-type AIHA, hemolysis usually ceases within 3 wk; however, a positive Coombs' test may persist for > 1 yr. With hapten-mediated AIHA, hemolysis ceases when the drug is cleared from the plasma. Corticosteroids have only little effect in drug-induced hemolysis; infusions of immune globulin may be more effective.

Corticosteroids (eg, prednisone 1 mg/kg po once/day or higher doses) are the treatment of choice in idiopathic warm antibody AIHA. In very severe hemolysis, an initial loading dose of 100 to 200 mg is recommended. Most patients have an excellent response, which in about one third is sustained after 12 to 20 wk of therapy. When stable RBC values are achieved, corticosteroids are tapered slowly. In patients who relapse after corticosteroid cessation or who are not helped by corticosteroids, splenectomy is done. About one third to one half of patients have a sustained response after splenectomy. In cases of fulminant hemolysis, plasma exchange has been used. For less severe but uncontrolled hemolysis, immune globulin infusions have provided temporary control. Long-term management with immunosuppressants (including cyclosporine) has been effective in patients in whom corticosteroids and splenectomy have been ineffective.

The presence of panagglutinating antibodies in warm antibody hemolytic anemia makes cross-matching of donor blood difficult. In addition, transfusions often superimpose an alloantibody on the autoantibody, accelerating hemolysis. Thus, transfusions should be avoided whenever possible. When necessary, they should be given only in small aliquots (100 to 200 mL over 1 to 2 h, with monitoring for hemolysis).

Cold agglutinin disease: Treatment is largely supportive in acute cases, because the anemia may be self-limited. In chronic cases, treatment of the underlying disorder often controls the anemia. However, in idiopathic chronic cases, mild anemia (Hb, 9 to 10 g/dL) may persist for life. Avoidance of cold exposure is often helpful. Splenectomy is of no value. Immunosuppressants have only modest effectiveness. Transfusions should be given sparingly, with the blood warmed through an on-line warmer. Because the

autologous RBCs have already survived the autoantibodies, autologous cell survival is better than that of transfused cells, limiting the efficacy of transfusion.

In PCH, therapy consists of strict avoidance of exposure to cold. Splenectomy is of no value. Immunosuppressants have been effective but should be restricted to patients with progressive or idiopathic cases. Treatment of concomitant syphilis may cure PCH.

Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disorder characterized by intravascular hemolysis and hemoglobinuria, the latter accentuated during sleep. Leukopenia, thrombocytopenia, and episodic crises are common. Diagnosis requires flow cytometry. Treatment is supportive.

PNH is most common among men in their 20s, but it occurs in both sexes and at any age.

Etiology

PNH is an acquired genetic mutation resulting in a membrane defect in stem cells and their progeny, including RBCs, WBCs, and platelets. It results in unusual sensitivity to normal (C3) in the plasma, leading to ongoing intravascular hemolysis of RBCs and diminished marrow production of WBCs and platelets. The defect is a missing glycosyl-phosphatidylinositol anchor for membrane proteins caused by an abnormality of the *PIG-A* gene, which is located on the X chromosome.

Pathophysiology

Protracted urinary Hb loss may result in iron deficiency. Patients are strongly predisposed to both venous and arterial thrombi, including the Budd-Chiari syndrome. Thrombi are commonly fatal. Some patients with PNH develop aplastic anemia, and some with aplastic anemia develop PNH.

Crises may be precipitated by infection, iron use, vaccination, or menstruation. Abdominal and lumbar pain and symptoms of severe anemia may occur; gross hemoglobinuria and splenomegaly are common.

Diagnosis

• Flow cytometry

• Possibly acid hemolysis test (Ham's test)

PNH is suspected in patients who have typical symptoms of anemia or unexplained normocytic anemia with intravascular hemolysis, particularly if leukopenia or thrombocytopenia is present. Historically, if PNH was suspected, the sugar-water test was usually the first test done; it relies on enhanced hemolysis of C3-dependent systems in isotonic solutions of low ionic strength, is simple to do, and is sensitive. However, the test is nonspecific; positive results require confirmation by further testing. The most sensitive and specific test is determination of the absence of specific RBC or WBC membrane proteins (CD59 and CD55) by flow cytometry. An alternative is the acid hemolysis test (Ham's test). Hemolysis usually occurs if blood is acidified with HCl, incubated for 1 h, and centrifuged. Bone marrow examination is not necessary but, if done to exclude other disorders, usually shows marrow hypoplasia. Gross hemoglobinuria is common during crises, and the urine may contain hemosiderin.

Treatment

• Supportive measures

• Possibly monoclonal antibody

Treatment is largely symptomatic. However, a new monoclonal antibody that is a terminal complement inhibitor, eculizumab, has reduced transfusion requirements, thromboembolism, and symptoms.

Supportive measures include corticosteroids, androgen hormones, iron and folate supplementation, and sometimes transfusions and stem cell transplantation. Empiric use of corticosteroids (eg, prednisone 20 to 40 mg po once/day) controls symptoms and stabilizes RBC values in > 50% of patients. Androgenic hormones and recombinant erythropoietin to stimulate hematopoiesis have been used in some patients. Generally, transfusions are reserved for crises. Transfusions containing plasma (and C3) should be avoided. Washing RBCs with saline before transfusion is no longer necessary. Heparin followed by warfarin may be required for thromboses but should be used cautiously. Oral iron and folate supplements may be necessary. Most cases can be managed by these supportive measures for years to decades. Allogenic stem cell transplantation has been successful in a small number of cases.

Traumatic Hemolytic Anemia

(Microangiopathic Hemolytic Anemia)

Traumatic hemolytic anemia is intravascular hemolysis caused by excessive shear or turbulence in the circulation.

Trauma may originate outside the vessel, as in skeletal impact, eg, repetitive foot striking (march hemoglobinuria) or from karate or bongo playing; within the heart across a pressure gradient, as in calcific aortic stenosis or with faulty aortic valve prostheses; in arterioles, as in severe (especially malignant) hypertension, some malignant tumors, or polyarteritis nodosa; or in end arterioles, often across fibrin deposits, as in thrombotic thrombocytopenic purpura and disseminated intravascular coagulation. The trauma causes odd-shaped RBC fragments (eg, triangles, helmet shapes) called schistocytes in the peripheral blood; their appearance on the peripheral smear is diagnostic. The small schistocytes cause low MCV and high RBC distribution width (the latter reflecting the anisocytosis).

Treatment addresses the underlying process. Iron deficiency anemia occasionally is superimposed on the hemolysis as a result of chronic hemosiderinuria and, when present, responds to iron-replacement therapy.

Hereditary Spherocytosis and Hereditary Elliptocytosis

Hereditary spherocytosis and hereditary elliptocytosis are congenital RBC membrane disorders. Symptoms, generally milder in hereditary elliptocytosis, include variable degrees of anemia, jaundice, and splenomegaly. Diagnosis requires demonstration of increased RBC osmotic fragility and a negative direct antiglobulin test. Rarely, patients < 45 yr with symptomatic disease require splenectomy.

Hereditary spherocytosis (chronic familial icterus; congenital hemolytic jaundice; familial spherocytosis; spherocytic anemia) is an autosomal dominant disease with variable gene penetrance. It is characterized by hemolysis of spheroidal RBCs and anemia.

Hereditary elliptocytosis (ovalocytosis) is a rare autosomal dominant disorder in which RBCs are oval or elliptical. Hemolysis is usually absent or slight, with little or no anemia; splenomegaly is often present.

Pathophysiology

Alterations in membrane proteins cause the RBC abnormalities in both disorders. In hereditary spherocytosis, the cell membrane surface area is decreased disproportionately to the intracellular content. The decreased surface area of the cell impairs the flexibility needed for the cell to traverse the spleen's microcirculation, causing intrasplenic hemolysis. In hereditary elliptocytosis, genetic mutations result in weakness of the cytoskeleton of the cell, leading to deformation of the cell. The abnormally shaped RBCs are taken up and destroyed by the spleen.

Symptoms and Signs

Symptoms and signs of hereditary spherocytosis are usually mild, and the anemia may be so well compensated that it is not recognized until an intercurrent viral illness transiently decreases RBC

production, simulating an aplastic crisis. However, these episodes are self-limited, resolving with resolution of the infection. Moderate jaundice and symptoms of anemia are present in severe cases. Splenomegaly is almost invariable but only rarely causes abdominal discomfort. Hepatomegaly may be present. Cholelithiasis (pigment stones) is common and may be the presenting symptom. Congenital skeletal abnormalities (eg, tower-shaped skull, polydactylism) occasionally occur. Although usually one or more family members have had symptoms, several generations may be skipped because of variations in the degree of gene penetrance.

Clinical features of hereditary elliptocytosis are similar to those of hereditary spherocytosis but tend to be milder.

Diagnosis

• RBC fragility assay, RBC autohemolysis assay, and direct antiglobulin test

These disorders are suspected in patients with unexplained hemolysis, particularly if splenomegaly, a family history of similar manifestations, or suggestive RBC indices are present. Because RBCs are spheroidal and the MCV is normal, the mean corpuscular diameter is below normal, and RBCs resemble microspherocytes. MCHC is increased. Reticulocytosis of 15 to 30% and leukocytosis are common.

If these disorders are suspected, the RBC osmotic fragility test (which mixes RBCs with varying concentrations of saline), the RBC autohemolysis test (which measures the amount of spontaneous hemolysis occurring after 48 h of sterile incubation), and, to rule out spherocytosis due to autoimmune hemolytic anemia, the direct antiglobulin (Coombs') test are done. RBC fragility is characteristically increased, but in mild cases, it may be normal unless sterile defibrinated blood is first incubated at 37° C for 24 h. RBC autohemolysis is increased and can be corrected by the addition of glucose. The direct antiglobulin test results are negative.

Treatment

• Sometimes splenectomy

Splenectomy, after appropriate vaccination, is the only specific treatment for either disorder but is rarely needed. It is indicated in patients < 45 yr with Hb persistently < 10 g/dL, jaundice or biliary colic, or persistent aplastic crisis. If the gallbladder has stones or other evidence of cholestasis, it should be removed during splenectomy. Although spherocytosis persists after splenectomy, the cells survive longer in the circulation. Usually, symptoms resolve and anemia and reticulocytosis decrease. However, RBC fragility remains high.

Stomatocytosis and Anemia Caused by Hypophosphatemia

Stomatocytosis (presence of cup- or bowl-shaped RBCs) and hypophosphatemia are RBC membrane abnormalities causing hemolytic anemia.

Stomatocytosis: Stomatocytosis is a rare condition of RBCs in which a mouth-like or slitlike pattern replaces the normal central zone of pallor. These cells are associated with congenital and acquired hemolytic anemia. The symptoms result from the anemia.

The rare congenital stomatocytosis, which shows autosomal dominant inheritance, causes a severe hemolytic anemia presenting very early in life. The RBC membrane is hyperpermeable to monovalent cations (Na and K); movement of divalent cations and anions is normal. About 20 to 30% of circulating RBCs are stomatocytic; RBC fragility is increased, as is autohemolysis with inconstant correction with glucose. Splenectomy ameliorates anemia in some cases.

Acquired stomatocytosis with hemolytic anemia occurs primarily with recent excessive alcohol ingestion. Stomatocytes in the peripheral blood and hemolysis disappear within 2 wk of alcohol withdrawal.

Anemia caused by hypophosphatemia: RBC pliability varies according to intracellular ATP levels.

Because the serum phosphate concentration affects RBC ATP levels, serum phosphate level < 0.5 mg/dL (< 0.16 mmol/L) depletes RBC ATP; the complex metabolic sequelae of hypophosphatemia also include 2,3-diphosphoglyceric acid depletion, a shift to the left in the O_2 dissociation curve, decreased glucose utilization, and increased lactate production. The resultant rigid, nonyielding RBCs are susceptible to injury in the capillary circulatory bed, leading to hemolysis and small, sphere-shaped RBCs (microspherocytosis).

Severe hypophosphatemia may occur in alcohol withdrawal, diabetes mellitus, refeeding after starvation, the recovery (diuretic) phase after severe burns, hyperalimentation, severe respiratory alkalosis, and in uremic patients receiving dialysis who are taking antacids. Phosphate supplements prevent or reverse the anemia and are considered for patients at risk of or who have hypophosphatemia.

Embden-Meyerhof Pathway Defects

Embden-Meyerhof pathway defects are autosomal recessive RBC metabolic disorders that cause hemolytic anemia.

Pyruvate kinase deficiency is one such enzyme defect. In all of these pathway defects, hemolytic anemia occurs only in homozygotes, and the exact mechanism of hemolysis is unknown. Spherocytes are absent, but small numbers of irregularly shaped spheres may be present. In general, assays of ATP and diphosphoglycerate help identify any metabolic defect and localize the defective sites for further analysis. There is no specific therapy for these hemolytic anemias, although most patients require no treatment other than supplemental folate 1 mg po once/day during acute hemolysis. Hemolysis and anemia persist after splenectomy, although some improvement may occur, particularly in patients with pyruvate kinase deficiency.

Glucose-6-Phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked enzymatic defect common in blacks that can result in hemolysis after acute illnesses or intake of oxidant drugs (including salicylates and sulfonamides). Diagnosis is based on assay for G6PD, although tests are often falsely negative during acute hemolysis. Treatment is supportive.

The only important defect in the hexose monophosphate shunt pathway is caused by G6PD deficiency. Over 100 mutant forms of the enzyme have been identified. Clinically, the most common form is the drug-sensitive variety. This X-linked disorder is fully expressed in males and homozygous females and is variably expressed in heterozygous females. This defect occurs in about 10% of black males and in < 10% of black females in the US and in lower frequencies among people with ancestors from the Mediterranean basin (eg, Italians, Greeks, Arabs, Sephardic Jews).

Pathophysiology

G6PD deficiency reduces energy available to maintain the integrity of the red cell membrane, which shortens RBC survival.

Hemolysis selectively affects older RBCs among affected blacks and among most affected whites. Hemolysis occurs commonly after fever, acute viral and bacterial infections, and diabetic acidosis. Less commonly, hemolysis occurs after exposure to drugs or to other substances that produce peroxide and cause oxidation of Hb and RBC membranes. These drugs and substances include primaquine, salicylates, sulfonamides, nitrofurans, phenacetin, naphthalene, some vitamin K derivatives, dapsone, phenazopyridine, nalidixic acid, methylene blue, and, in some whites, fava beans. Whether continued use of the offending drug leads to a compensated hemolytic state or lethal hemolysis depends on the degree of G6PD deficiency and the oxidant potential of the drug. Chronic congenital hemolysis (without drug use) occurs in some whites. Because older cells are selectively destroyed in blacks, hemolysis is usually self-limited, affecting < 25% of RBC mass; in whites, the deficiency is more severe, and profound hemolysis may lead to hemoglobinuria and acute renal failure.

Diagnosis

• G6PD assay

The diagnosis is considered in patients with acute hemolysis, particularly black males. G6PD assay is done. Anemia, jaundice, and reticulocytosis develop during hemolysis. Heinz bodies, possibly particles of dead cytoplasm or denatured Hb, may be visible early during the hemolytic episode but do not persist in patients with an intact spleen because they are removed by it. A specific diagnostic clue is the presence in the peripheral blood of RBCs that appear to have had one or more bites (1-µm wide) taken from the cell periphery (bite cells), possibly as a result of Heinz body removal by the spleen. Many screening tests are available. However, during and immediately after a hemolytic episode, tests may yield false-negative results because of destruction of the older, more deficient RBCs and the presence of reticulocytes rich in G6PD. Specific enzyme assays are the best diagnostic tests.

Treatment

During acute hemolysis, treatment is supportive; transfusions are rarely needed. Patients are advised to avoid drugs or substances that initiate hemolysis.

Sickle Cell Disease

(Hb S Disease)

Sickle cell disease (a hemoglobinopathy—see Sidebar 106-1) causes a chronic hemolytic anemia occurring almost exclusively in blacks, caused by homozygous inheritance of Hb S. Sickle-shaped RBCs clog capillaries, causing organ ischemia. Acute exacerbations (crises) may develop frequently. Infection, bone marrow aplasia, or lung involvement (acute chest syndrome) can develop acutely and be fatal. Normocytic hemolytic anemia is characteristic. Diagnosis requires Hb electrophoresis. Crises are treated with analgesics and other supportive measures. Transfusions are occasionally required. Vaccines against bacterial infections, prophylactic antibiotics, and aggressive treatment of infections prolong survival. Hydroxyurea may decrease the frequency of crises.

Homozygotes (about 0.3% of blacks in the US) have sickle cell anemia; heterozygotes (8 to 13% of blacks) are typically not anemic.

Pathophysiology

In Hb S, valine is substituted for glutamic acid in the 6th amino acid of the β chain. Oxygenated Hb S is much less soluble than oxygenated Hb A; it forms a semisolid gel that causes RBCs to deform in a sickle shape at sites of low PO_2. Distorted, inflexible RBCs adhere to vascular endothelium and plug small arterioles and capillaries, which leads to infarction. Venous plugging predisposes to thromboses. Because sickled RBCs are fragile, the mechanical trauma of circulation causes hemolysis. Chronic compensatory marrow hyperactivity deforms the bones.

Acute exacerbations: Acute exacerbations (crises) occur intermittently, often for no known reason. In some cases, fever, viral infection, or local trauma appears to precipitate a crisis.

Sidebar 106-1 Hemoglobinopathies

Hb molecules consist of polypeptide chains whose chemical structure is genetically controlled. The normal adult Hb molecule (Hb A) consists of 2 pairs of chains designated α and β. Normal blood also contains a ≤ 2.5% concentration of Hb A_2 (composed of α and δ chains). Fetal Hb (Hb F, which has γ chains in the place of β chains) gradually decreases, particularly in the first months of life, until it makes up < 2% of total Hb in adults (see Hemoglobinopathies on p. 2636). Hb F concentration increases in certain disorders of Hb synthesis and in aplastic and myeloproliferative states.

Some hemoglobinopathies result in anemias that are severe in patients who are homozygous but mild in

patients who are heterozygous. Some patients are heterozygous for 2 such abnormalities and have anemia with characteristics of both traits.

Different Hbs, as distinguished by electrophoretic mobility, are alphabetically designated in order of discovery (eg, A, B, C), although the first abnormal Hb, sickle cell Hb, was designated Hb S. Structurally different Hbs with the same electrophoretic mobility are named for the city or location in which they were discovered (eg, Hb S Memphis, Hb C Harlem). Standard description of a patient's Hb composition places the Hb of greatest concentration first (eg, AS in sickle cell trait).

In the US, important anemias are caused by defective synthesis of Hb S or Hb C and the thalassemias, and immigration of Southeast Asians has made Hb E disease common.

Painful crisis is the most common type; it is caused by ischemia and infarction, typically of the bones, but also of the spleen, lung, or kidney.

Aplastic crisis occurs when marrow erythropoiesis slows during acute infection (especially viral), during which an acute erythroblastopenia may occur.

Acute chest syndrome results from pulmonary microvascular occlusion and is a common cause of death, with mortality rates of up to 10%. It occurs in all age groups but is most common in childhood. Repeated episodes predispose to chronic pulmonary hypertension.

In children, acute sequestration of sickled cells in the spleen may occur, exacerbating anemia.

Priapism, a serious complication that can cause erectile dysfunction, is most common in young men.

Complications: Long-term consequences include impaired growth and development. Increased susceptibility to infection, particularly pneumococcal and *Salmonella* infections (including *Salmonella* osteomyelitis), also results. These infections are especially common in early childhood and can be rapidly fatal.

Other consequences include ischemic stroke, CNS vasculitis, avascular necrosis of the hips, renal concentrating defects, renal failure, heart failure, and pulmonary fibrosis.

Symptoms and Signs

Most symptoms occur only in patients who are homozygous and result from anemia and vaso-occlusive events resulting in tissue ischemia and infarction. Anemia is usually severe but varies highly among patients; mild jaundice and pallor are common.

Patients may be poorly developed and often have a relatively short trunk with long extremities and a tower-shaped skull. Hepatosplenomegaly is common in children, but because of repeated infarctions and subsequent fibrosis (autosplenectomy), the spleen in adults is commonly very small. Cardiomegaly and systolic ejection (flow) murmurs are common. Cholelithiasis and chronic punched-out ulcers around the ankles are common.

Painful crisis causes severe pain in long bones (eg, pretibial pain), the hands and feet (eg, hand-foot syndrome), and joints. Joint pain may result from hemarthrosis or avascular necrosis of the femoral head. Severe abdominal pain may develop with or without vomiting and, when due to sickling itself, is usually accompanied by back and joint pain.

Acute chest syndrome is characterized by sudden onset of fever, chest pain, and pulmonary infiltrates. The infiltrates begin in the lower lobes, are bilateral in one third of cases, and may be accompanied by pleural effusion. It may follow bacterial pneumonia. Hypoxemia may develop rapidly, causing dyspnea.

Heterozygotes: Patients who are heterozygous (Hb AS) do not experience hemolysis, painful crises, or thrombotic complications except possibly during hypoxic conditions (eg, at high altitudes, during sudden

decompression in airplanes). However, rhabdomyolysis and sudden death may occur during sustained, exhausting exercise. Impaired ability to concentrate urine (hyposthenuria) is common. Unilateral hematuria (by unknown mechanisms and usually from the left kidney) can occur but is self-limited. Typical renal papillary necrosis can occur but is less common than among homozygous patients.

Diagnosis

• DNA testing (prenatal diagnosis)

• Peripheral smear

• Solubility testing

• Hb electrophoresis (or thin-layer isoelectric focusing)

The type of testing done depends on the age of the patient. DNA testing can be used for prenatal diagnosis or to confirm a diagnosis of the sickle cell genotype. Screening of neonates is available in most US states and involves Hb electrophoresis. Screening and diagnosis in children and adults involve examination of the peripheral smear, Hb solubility testing, and Hb electrophoresis.

Prenatal screening: The sensitivity of prenatal diagnosis has been greatly improved with the availability of the PCR technique. It is recommended for families at risk for sickle cell (eg, couples with medical or family histories of anemia or of suggestive ethnic background). DNA samples can be obtained by chorionic villus sampling at 8 to 10 wk gestation. Amniotic fluid can also be tested at 14 to 16 wk. Diagnosis is important for genetic counseling.

Newborn screening: Universal testing is currently recommended and is frequently one of a battery of newborn screening tests. To distinguish between Hbs F, S, A, and C, the recommended tests are Hb electrophoresis using cellulose acetate or acid citrate agar, thin-layer isoelectric focusing, or Hb fractionation by high performance liquid chromatography (HPLC). Repeat testing at age 3 to 6 mo may be necessary for confirmation. Solubility testing for Hb S is unreliable during the first few months of life.

Screening and diagnosis of children and adults: Patients with a family history of sickle cell disease or trait should be screened with peripheral smear, Hb solubility testing, and Hb electrophoresis.

Patients with symptoms or signs suggesting the disorder or its complications (eg, poor growth, acute and unexplained bone pain, aseptic necrosis of the femoral head, unexplained hematuria), and black patients with normocytic anemia (particularly if hemolysis is present) require laboratory tests for hemolytic anemia (see p. 936), Hb electrophoresis, and examination of RBCs for sickling. If sickle cell disease is present, RBC count is usually between 2 and 3 million/μL with Hb reduced proportionately; cells are normocytic (microcytosis suggests a concomitant α-thalassemia). Nucleated RBCs frequently appear in the peripheral blood, and reticulocytosis ≥ 10% is common. Dry-stained smears may show sickled RBCs (crescent-shaped, often with elongated or pointed ends).

The homozygous state is differentiated from other sickle hemoglobinopathies by electrophoresis showing only Hb S with a variable amount of Hb F. The heterozygote is differentiated by the presence of more Hb A than Hb S on electrophoresis. Hb S must be distinguished from other Hb with a similar electrophoretic pattern by showing the pathognomonic RBC morphology.

Bone marrow examination is not used for diagnosis. If it is done to differentiate other anemias, it shows hyperplasia, with normoblasts predominating; bone marrow may become aplastic during sickling or severe infections. ESR, if done to exclude other disorders (eg, juvenile RA causing hand and foot pain), is low. Incidental findings on skeletal x-rays may include widening of the diploic spaces of the skull and a sun-ray appearance of the diploic trabeculations. The long bones often show cortical thinning, irregular densities, and new bone formation within the medullary canal. Unexplained hematuria, even among patients not suspected of having sickle cell disease, should prompt consideration of sickle cell trait.

Evaluation of exacerbations: If patients with known sickle cell disease have acute exacerbations,

including pain, fever, or other symptoms of infection, aplastic crisis is considered and CBC and reticulocyte count are done. Reticulocyte count < 1% suggests aplastic crisis, particularly when Hb decreases below the patient's usual level. In a painful crisis without aplasia, WBC count rises, often with a shift to the left, particularly during bacterial infection. Platelet count usually increases. If measured, serum bilirubin is usually elevated (eg, 2 to 4 mg/dL [34 to 68 µmol/L]), and urine may contain urobilinogen.

In patients with chest pain or difficulty breathing, acute chest syndrome and pulmonary embolism are considered; chest x-ray and pulse oximetry are necessary. Hypoxemia or pulmonary parenchymal infiltrates on chest x-ray suggest acute chest syndrome or pneumonia. Hypoxemia without pulmonary infiltrates suggests pulmonary embolism.

In patients with fever, infection and acute chest syndrome are considered; cultures, chest x-ray, and other appropriate diagnostic tests are done.

Prognosis

The life span of homozygous patients has steadily increased to > 50 yr. Common causes of death are acute chest syndrome, intercurrent infections, pulmonary emboli, infarction of a vital organ, and renal failure.

Treatment

• Broad-spectrum antibiotics (for infection)

• Analgesics and IV hydration (for vasoocclusive pain crisis)

• Sometimes transfusions

• Immunizations, folate supplementation, and hydroxyurea (for health maintenance)

Treatment includes regular health maintenance measures as well as specific treatment of the complications as they arise. Complications are treated supportively. No effective in vivo anti-sickling drug is available. Splenectomy is valueless. Stem cell transplantation has been curative in a small number of patients but has a 5 to 10% mortality rate and so is not commonly done. Gene therapy offers hope for a cure, but it is still under study.

Indications for hospitalization include suspected serious (including systemic) infection, aplastic crisis, acute chest syndrome, and, often, intractable pain or the need for transfusion. Fever alone may not be a reason to hospitalize. However, patients who appear acutely ill and have a temperature > 38°C should be admitted so that cultures can be obtained from multiple areas and IV antibiotics can be given.

Antibiotics: Patients with suspected serious bacterial infections or acute chest syndrome require broad-spectrum antibiotics immediately.

Analgesics: Painful crises are managed with liberal administration of analgesics, usually opioids. IV morphine (continuous or bolus) is effective and safe; meperidine is avoided. Although dehydration contributes to sickling and may precipitate crises, it is unclear whether vigorous hydration is helpful during crises. Nevertheless, maintaining normal intravascular volume has been a mainstay of therapy. During crises, pain and fever may persist for as long as 5 days.

Transfusion: Transfusion is given in many situations in which its efficacy has not been demonstrated. However, routine transfusion therapy is indicated for prevention of recurrent cerebral thrombosis, especially in children. Transfusion is usually done when Hb is < 5 g/dL. Specific indications include acute splenic sequestration, aplastic crises, cardiopulmonary symptoms or signs (eg, high-output heart failure, hypoxemia with PO_2 < 65 mm Hg), preoperative use, priapism, and life-threatening events that would benefit from improved O_2 delivery (eg, sepsis, severe infection, acute chest syndrome, stroke, acute organ ischemia). Transfusion is not helpful during an uncomplicated painful crisis; however, it may break

a cycle of closely spaced painful crises. Transfusion may be needed in pregnancy.

Partial exchange transfusion is usually preferred to simple transfusion if routine or multiple transfusions are necessary. It can be done with modern apheresis machines. If the initial Hb is low (< 7 g/dL), this process cannot be initiated before first transfusing red cells. Partial exchange transfusion minimizes iron accumulation and hyperviscosity.

Health maintenance: For long-term management the following interventions have reduced mortality, particularly during childhood:

• Pneumococcal, *Haemophilus influenzae*, and meningococcal vaccines

• Early identification and treatment of serious bacterial infections

• Prophylactic antibiotics, including continuous prophylaxis with oral penicillin from age 4 mo to 6 yr

• Use of hydroxyurea and folate supplementation

Supplemental folate, 1 mg po once/day, is usually prescribed.

Hydroxyurea, by increasing Hb F and thereby reducing sickling, decreases painful crises (by 50%) and decreases acute chest syndrome and transfusion requirements. The dose of hydroxyurea is variable and is adjusted to increase Hb F. Hydroxyurea may be more effective when combined with erythropoietin (eg, 40,000 to 60,000 units/wk). However, hydroxyurea is a leukemogen and causes neutropenia and thrombocytopenia. It is also a teratogen and should not be given to females of child-bearing age.

Erythropoietin use in patients with anemia unrelated to chemotherapy has been associated with increased frequency of venous thromboembolic events and cardiopulmonary complications (eg, MI); it is generally not helpful in patients with sickle cell disease.

Hemoglobin C Disease

Hemoglobin C disease is a hemoglobinopathy (see Sidebar 106-1) that causes symptoms similar to those of sickle cell disease, but milder.

Of blacks in the US, 2 to 3% have the trait, which is asymptomatic. Symptoms in homozygotes are usually similar to those of sickle cell disease, but milder. However, the abdominal crises of sickle cell disease do not occur, and the spleen is usually enlarged. Splenic sequestration is possible.

Hemoglobin C disease is suspected in all patients with a family history and in black patients with clinical features suggesting sickle cell disease, particularly in adults with splenomegaly. The anemia is usually mild but can be moderately severe. The smear is normocytic, with 30 to 100% target cells, spherocytes, and, rarely, crystal-containing RBCs. Nucleated RBCs may be present. The RBCs do not sickle. On electrophoresis, the Hb is type C. In heterozygotes, the only laboratory abnormality is centrally targeted RBCs.

No specific treatment is recommended. Anemia usually is not severe enough to require blood transfusion.

Hemoglobin S-C Disease

Hemoglobin S-C disease is a hemoglobinopathy (see Sidebar 106-1) that causes symptoms similar to those of sickle cell disease, but milder.

Because 10% of blacks carry the Hb S trait, the heterozygous S-C combination is more common than homozygous Hb C disease. The anemia in Hb S-C disease is milder than the anemia in sickle cell disease; some patients even have normal Hb levels. Most symptoms are those of sickle cell disease, but symptoms are usually less frequent and less severe. However, gross hematuria, retinal hemorrhages, and aseptic necrosis of the femoral head are common. Hb S-C disease is suspected in patients whose clinical

features suggest sickle cell disease or whose RBCs demonstrate sickling. Stained blood smears show target cells and a rare sickle cell. Sickling is identified in a sickling preparation, and Hb electrophoresis establishes the diagnosis. Treatment can be similar to that of sickle cell disease but is determined by severity of symptoms.

Hemoglobin E Disease

Homozygous Hb E disease (a hemoglobinopathy—see Sidebar 106-1) causes a mild hemolytic anemia, usually without splenomegaly.

Hb E is the 3rd most prevalent Hb worldwide (after Hb A and Hb S), primarily in black and Southeast Asian (> 15% incidence of homozygous disease) populations, although rarely in Chinese populations. Heterozygotes (Hb AE) are asymptomatic. Patients heterozygous for Hb E and β-thalassemia have a hemolytic disease more severe than S-thalassemia or homozygous Hb E disease and usually have splenomegaly.

In heterozygotes (Hb AE), routine laboratory test results of peripheral blood are normal. In homozygotes, a mild microcytic anemia with prominent target cells exists. Diagnosis of Hb E disorders is by Hb electrophoresis. Treatment in homozygous patients with severe disease usually involves chronic transfusions.

Thalassemias

(Mediterranean Anemia; Thalassemia Major and Minor)

Thalassemias are a group of inherited microcytic, hemolytic anemias characterized by defective Hb synthesis. They are particularly common in people of Mediterranean, African, and Southeast Asian ancestry. Symptoms and signs result from anemia, hemolysis, splenomegaly, bone marrow hyperplasia, and, if there have been multiple transfusions, iron overload. Diagnosis is based on genetic tests and quantitative Hb analysis. Treatment for severe forms may include transfusion, splenectomy, chelation, and stem cell transplantation.

Pathophysiology

Thalassemia (a hemoglobinopathy—see Sidebar 106-1) is among the most common inherited disorders of Hb production. It results from unbalanced Hb synthesis caused by decreased production of at least one globin polypeptide chain (β, α, γ, δ).

β-Thalassemia results from decreased production of β-polypeptide chains. Inheritance is autosomal: Heterozygotes are carriers and have asymptomatic mild to moderate microcytic anemia (thalassemia minor); homozygotes (β-thalassemia major, or Cooley's anemia) develop severe anemia and bone marrow hyperactivity. β-δ-Thalassemia is a less common form of β-thalassemia in which δ-chain as well as β-chain production is impaired and which also has heterozygous and homozygous states.

α-Thalassemia, which results from decreased production of α-polypeptide chains, has a more complex inheritance pattern, because genetic control of α-chain synthesis involves 2 pairs of genes (4 genes). Heterozygotes for a single gene defect (α-thalassemia-2 [silent]) are usually clinically normal. Heterozygotes with defects in 2 of the 4 genes (α-thalassemia-1 [trait]) tend to develop mild to moderate microcytic anemia but no symptoms. Defects in 3 of the 4 genes more severely impairs α-chain production, resulting in the formation of tetramers of excess β chains (Hb H) or, in infancy, γ chains (Bart's Hb). Defects in all 4 genes are a lethal condition in utero, because Hb that lacks α chains does not transport O_2. In blacks, the gene frequency for α-thalassemia is about 25%; only 10% have defects in more than 2 genes.

Symptoms and Signs

Clinical features of thalassemias are similar but vary in severity. β-Thalassemia major manifests by age 1 to 2 yr with symptoms of severe anemia and transfusional and absorptive iron overload. Patients are

jaundiced, and leg ulcers and cholelithiasis occur (as in sickle cell anemia). Splenomegaly, often massive, is common. Splenic sequestration may develop, accelerating destruction of transfused normal RBCs. Bone marrow hyperactivity causes thickening of the cranial bones and malar eminences. Long bone involvement predisposes to pathologic fractures and impairs growth, possibly delaying or preventing puberty. Iron deposits in heart muscle may cause heart failure. Hepatic siderosis is typical, leading to functional impairment and cirrhosis. Patients with Hb H disease often have symptomatic hemolytic anemia and splenomegaly.

Diagnosis

• Evaluation for hemolytic anemia if suspected

• Peripheral smear

• Electrophoresis

• DNA testing (prenatal diagnosis)

Thalassemias are suspected in patients with a family history, suggestive symptoms or signs, or microcytic hemolytic anemia. If thalassemias are suspected, laboratory tests for microcytic and hemolytic anemias and quantitative Hb studies are done. Serum bilirubin, iron, and ferritin levels are increased.

In β-thalassemia major, anemia is severe, often with Hb ≤ 6 g/dL. RBC count is elevated relative to Hb because the cells are very microcytic. The blood smear is virtually diagnostic, with many nucleated erythroblasts; target cells; small, pale RBCs; and punctate and diffuse basophilia.

In quantitative Hb studies, elevation of Hb A_2 is diagnostic for β-thalassemia minor. In β-thalassemia major, Hb F is usually increased, sometimes to as much as 90%, and Hb A_2 is usually elevated to > 3%. The percentages of Hb F and Hb A_2 are generally normal in α-thalassemias, and the diagnosis of single or double gene defect thalassemias may be carried out with newer genetic tests and often is one of exclusion of other causes of microcytic anemia. Hb H disease can be diagnosed by demonstrating the fast-migrating Hb H or Bart's fractions on Hb electrophoresis. The specific molecular defect can be characterized but does not alter the clinical approach. Recombinant DNA approaches of gene mapping (particularly the PCR) have become standard for prenatal diagnosis and genetic counseling.

If bone marrow examination is done for anemia (eg, to exclude other causes), it shows marked erythroid hyperplasia. X-rays done for other reasons in patients with β-thalassemia major show changes due to chronic bone marrow hyperactivity. The skull may show cortical thinning, widened diploic space, a sun-ray appearance of the trabeculae, and a granular or ground-glass appearance. The long bones may show cortical thinning, marrow space widening, and areas of osteoporosis. The vertebral bodies may have a granular or ground-glass appearance. The phalanges may appear rectangular or biconvex.

Prognosis

Life expectancy is normal for people with β-thalassemia minor or α-thalassemia minor. The outlook for people with Hb H disease varies. Life expectancy is decreased in people with β-thalassemia major; only some live to puberty or beyond.

Treatment

• Sometimes splenectomy

• Sometimes RBC transfusion and chelation therapy

• Rarely allogeneic stem cell transplantation

People with α- and β-thalassemia minor require no treatment. Splenectomy may be helpful if Hb H

disease causes severe anemia or splenomegaly.

Children with β-thalassemia major should receive as few transfusions as possible to avoid iron overload. However, suppression of abnormal hematopoiesis by periodic RBC transfusion may be valuable in severely affected patients. To prevent or delay iron overload, excess (transfusional) iron must be removed (eg, via chronic iron-chelation therapy). Splenectomy may help decrease transfusion requirements for patients with splenomegaly. Allogeneic stem cell transplantation has been successful, but the requirement for a histocompatible match, mortality and morbidity of the procedure, and lifelong requirement for immunosuppression have limited its usefulness.

Hemoglobin S-β-Thalassemia Disease

Hemoglobin S-β-thalassemia disease is a hemoglobinopathy (see Sidebar 106-1) that causes symptoms similar to those of sickle cell disease, but milder.

Because of the increased frequency of both Hb S and β-thalassemia genes in similar population groups, inheritance of both defects is relatively common. Clinically, the disorder causes symptoms of moderate anemia and signs of sickle cell anemia, which are usually less frequent and less severe than those of sickle cell disease. Mild to moderate microcytic anemia is usually present along with some sickled RBCs on stained blood smears. Diagnosis requires quantitative Hb studies. The Hb A_2 is > 3%. Hb S predominates on electrophoresis, and Hb A is decreased or absent. Hb F increase is variable. Treatment, if necessary, is the same as for sickle cell disease.

Chapter 107. Neutropenia and Lymphocytopenia

Introduction

Leukopenia is a reduction in the circulating WBC count to < 4000/µL. It is usually characterized by a reduced number of circulating neutrophils, although a reduced number of lymphocytes, monocytes, eosinophils, or basophils may also contribute. Thus, immune function is generally greatly decreased.

Neutropenia is a reduction in blood neutrophil count to < 1500/µL in whites and < 1200/µL in blacks. It is more serious when accompanied by monocytopenia and lymphocytopenia. Lymphocytopenia, in which the total number of lymphocytes is < 1000/µL in adults, is not always reflected in the total WBC count, because lymphocytes account for only 20 to 40% of the count.

Neutropenia

(Agranulocytosis; Granulocytopenia)

Neutropenia is a reduction in the blood neutrophil count. If it is severe, the risk and severity of bacterial and fungal infections increase. Focal symptoms of infection may be muted, but fever is present during most serious infections. Diagnosis is by WBC count, but evaluation requires identification of the cause. If fever is present, infection is presumed, and immediate, empiric broad-spectrum antibiotics are necessary. Treatment with granulocyte-macrophage colony-stimulating factor or granulocyte colony-stimulating factor is sometimes helpful.

Neutrophils (granulocytes) are the body's main defense against bacterial and fungal infections. When neutropenia is present, the inflammatory response to such infections is ineffective. Normal lower limit of the neutrophil count (total WBC × % neutrophils and bands) is 1500/µL in whites and is somewhat lower in blacks (about 1200/µL).

Severity of neutropenia relates to the relative risk of infection:

• Mild (1000 to 1500/µL)

• Moderate (500 to 1000/µL)

• Severe (< 500/µL)

When neutrophil counts fall to < 500/µL, endogenous microbial flora (eg, in the mouth or gut) can cause infections. If the count falls to < 200/µL, inflammatory response may be nonexistent. Acute, severe neutropenia, particularly if another factor (eg, cancer) also impairs the immune system, predisposing to rapidly fatal infections. The integrity of the skin and mucous membranes, the vascular supply to tissue, and the nutritional status of the patient also influence the risk of infections.

The most frequently occurring pyogenic infections in patients with profound neutropenia are

• Cellulitis

• Liver abscesses

• Furunculosis

• Pneumonia

• Septicemia

Vascular catheters and other puncture sites confer extra risk of skin infections; the most common bacterial causes are coagulase-negative staphylococci and *Staphylococcus aureus*. Stomatitis, gingivitis, perirectal inflammation, colitis, sinusitis, paronychia, and otitis media often occur. Patients with prolonged

neutropenia after bone marrow transplantation or chemotherapy and patients receiving high doses of corticosteroids are predisposed to fungal infections.

Etiology

Acute neutropenia (occurring over hours to a few days) can develop from rapid neutrophil use or destruction or from impaired production. Chronic neutropenia (lasting months to years) usually arises from reduced production or excessive splenic sequestration.

Neutropenia also may be classified as due to an intrinsic defect in marrow myeloid cells or as secondary (due to factors extrinsic to marrow myeloid cells—see Table 107-1).

Neutropenia caused by intrinsic defects in myeloid cells or their precursors: This type of neutropenia is uncommon, but when present, the most common causes include

• Chronic idiopathic neutropenia

• Congenital neutropenia

Cyclic neutropenia is a rare congenital granulocytopoietic disorder, usually transmitted in an autosomal dominant fashion. It is characterized by regular, periodic oscillations in the number of peripheral neutrophils. The mean oscillatory period is 21 ± 3 days.

Severe congenital neutropenia (Kostmann's syndrome) is a rare disorder that occurs sporadically in the US and is characterized by an arrest in myeloid maturation at the promyelocyte stage of the bone marrow, resulting in an absolute neutrophil count of < 200/µL.

Chronic idiopathic neutropenia is a group of uncommon, poorly understood disorders involving stem cells committed to the myeloid series; RBC and platelet precursors are unaffected. The spleen is not enlarged. Chronic benign neutropenia is a type of chronic idiopathic neutropenia in which the rest of the immune system appears to remain intact; even with neutrophil counts < 200/µL, serious infections usually do not occur, probably because neutrophils are sometimes produced in adequate quantities in response to infection.

Neutropenia can also result from bone marrow failure due to rare syndromes (eg, cartilage-hair hypoplasia, Chediak-Higashi syndrome, dyskeratosis congenita, glycogen storage disease type IB, Shwachman-Diamond syndrome). Neutropenia is also a prominent feature of myelodysplasia (see p. 1014), where it may be accompanied by megaloblastoid features in the bone marrow, and of aplastic anemia (see p. 929) and can occur in dysgammaglobulinemia and paroxysmal nocturnal hemoglobinemia.

Secondary neutropenia: Secondary neutropenia can result from use of certain drugs, bone marrow infiltration or replacement, certain infections, or immune reactions. The most common causes include

• Drugs

• Infections

• Marrow infiltrative processes

[**Table 107-1.** Classification of Neutropenias]

Drug-induced neutropenia is one of the most common causes of neutropenia. Drugs can decrease neutrophil production through toxic, idiosyncratic, or hypersensitivity mechanisms or increase peripheral neutrophil destruction through immune mechanisms. Only the toxic mechanism (eg, with phenothiazines) produces dose-related neutropenia. Idiosyncratic reactions are unpredictable and occur with a wide variety of drugs, including alternative medicine preparations or extracts, and toxins. Hypersensitivity reactions are rare and occasionally involve anticonvulsants (eg, phenytoin, phenobarbital). These

reactions may last for only a few days or for months or years. Often, hepatitis, nephritis, pneumonitis, or aplastic anemia accompanies hypersensitivity-induced neutropenia. Immune-mediated drug-induced neutropenia, thought to arise from drugs that act as haptens to stimulate antibody formation, usually persists for about 1 wk after the drug is stopped. It may result from aminopyrine, propylthiouracil, penicillin, or other antibiotics. Severe dose-related neutropenia occurs predictably after cytotoxic cancer drugs or radiation therapy suppresses bone marrow production.

Neutropenia due to ineffective bone marrow production can occur in megaloblastic anemias caused by vitamin B_{12} or folate deficiency. Usually, macrocytic anemia and sometimes mild thrombocytopenia develop simultaneously.

Bone marrow infiltration by leukemia, myeloma, lymphoma, or metastatic solid tumors (eg, breast, prostate) can impair neutrophil production. Tumor-induced myelofibrosis may further exacerbate neutropenia. Myelofibrosis can also occur from granulomatous infections, Gaucher's disease, and radiation therapy. Hypersplenism of any cause can lead to moderate neutropenia, thrombocytopenia, and anemia.

Infections can cause neutropenia by impairing neutrophil production or by inducing immune destruction or rapid use of neutrophils. Sepsis is a particularly serious cause. Neutropenia that occurs with common childhood viral diseases develops during the first 1 to 2 days of illness and may persist for 3 to 8 days. Transient neutropenia may also result from virus- or endotoxemia-induced redistribution of neutrophils from the circulating to the marginal pool. Alcohol may contribute to neutropenia by inhibiting the neutrophilic response of the marrow during some infections (eg, pneumococcal pneumonia).

Chronic secondary neutropenia often accompanies HIV infection because of impaired production of neutrophils and accelerated destruction of neutrophils by antibodies. Autoimmune neutropenias may be acute, chronic, or episodic. They may involve antibodies directed against circulating neutrophils or neutrophil precursor cells. Most patients with autoimmune neutropenia have an underlying autoimmune disorder or lymphoproliferative disorder (eg, SLE, Felty's syndrome).

Symptoms and Signs

Neutropenia is asymptomatic until infection develops. Fever is often the only indication of infection. Focal symptoms may develop but are often subtle. Patients with drug-induced neutropenia due to hypersensitivity may have a fever, rash, and lymphadenopathy from the hypersensitivity.

Some patients with chronic benign neutropenia and neutrophil counts < 200/μL do not experience many serious infections. Patients with cyclic neutropenia or severe congenital neutropenia tend to have episodes of oral ulcers, stomatitis, or pharyngitis and lymph node enlargement during severe chronic neutropenia. Pneumonias and septicemia often occur.

Diagnosis

• Clinical suspicion (repeated or unusual infections)

• Confirmatory CBC with differential

• Evaluation for infection with cultures and imaging

• Identification of mechanism and cause of neutropenia

Neutropenia is suspected in patients with frequent, severe, or unusual infections or in patients at risk (eg, those receiving cytotoxic drugs or radiation therapy). Confirmation is by CBC with differential.

Evaluation for infection: The first priority is to determine whether an infection is present. Because infection may be subtle, physical examination systematically assesses the most common primary sites of infection: mucosal surfaces, such as the alimentary tract (gums, pharynx, anus); lungs; abdomen; urinary tract; skin and fingernails; venipuncture sites; and vascular catheters.

If neutropenia is acute, laboratory evaluation must proceed rapidly.

Cultures are the mainstay of evaluation. At least 2 sets of bacterial and fungal blood cultures are obtained from all febrile patients; if an indwelling IV catheter is present, cultures are obtained from the lumen and from a separate peripheral vein. Persistent or chronic drainage material is also cultured for fungi and atypical mycobacteria. Skin lesions are aspirated or biopsied for cytology and culture. Samples for urinalysis and urine cultures are obtained from all patients. If diarrhea is present, stool is evaluated for enteric bacterial pathogens and *Clostridium difficile* toxins.

Imaging studies are helpful. Chest x-rays are done on all patients. CT scan of the para-nasal sinuses may be helpful if symptoms or signs of sinusitis (eg, positional headache, upper tooth or maxillary pain, facial swelling, nasal discharge) are present. CT scan of the abdomen is usually done if symptoms (eg, pain) or history (eg, recent surgery) suggests an intra-abdominal infection.

Identification of cause: Next, mechanism and cause of neutropenia are determined. The history addresses all drugs, other preparations, and possible toxin exposure or ingestion. Physical examination addresses the presence of splenomegaly and signs of other underlying disorder (eg, arthritis, lymphadenopathy).

The most important test is bone marrow examination, which determines whether neutropenia is due to decreased marrow production or is secondary to increased destruction or use of the cells (determined by normal or increased production of the cells). Bone marrow may also indicate the specific cause of the neutropenia (eg, aplastic anemia, myelofibrosis, leukemia). Additional marrow studies (eg, cytogenetic analysis; special stains and flow cytometry for detecting leukemia, other malignant disorders, and infections) are obtained.

Further testing for the cause of neutropenia may be necessary, depending on the diagnoses suspected. In patients at risk of deficiency, levels of folate and vitamin B_{12} are determined. Testing for the presence of antineutrophil antibodies is done if immune neutropenia is suspected. Differentiation between neutropenia caused by certain antibiotics and infection can sometimes be difficult. The WBC count just before the start of antibiotic treatment usually reflects the change in blood count due to the infection.

Patients who have had chronic neutropenia since infancy and a history of recurrent fevers and chronic gingivitis have WBC counts with differential done 3 times/wk for 6 wk, so that periodicity suggestive of cyclic neutropenia can be evaluated. Platelet and reticulocyte counts are done simultaneously. Eosinophils, reticulocytes, and platelets frequently cycle synchronously with the neutrophils, whereas monocytes and lymphocytes may cycle out of phase.

Treatment

- Treatment of associated conditions (eg, infections, stomatitis)
- Sometimes antibiotic prophylaxis
- Myeloid growth factors
- Discontinuation of suspected etiologic agent (eg, drug)
- Sometimes corticosteroids
- Rarely splenectomy

Acute neutropenia: Suspected infections are always treated immediately. If fever or hypotension is present, serious infection is assumed, and empiric, high-dose, broad-spectrum antibiotics are given IV. Regimen selection is based on the most likely infecting organisms, the antimicrobial susceptibility of pathogens at that particular institution, and the regimen's potential toxicity. Because of the risk of creating resistant organisms, vancomycin is used only if gram-positive organisms resistant to other drugs are

suspected.

Indwelling vascular catheters can usually remain in place even if bacteremia is suspected or documented, but removal is considered if infections involve *S. aureus* or *Bacillus*, *Corynebacterium,* or *Candida* sp or if blood cultures are persistently positive despite appropriate antibiotics. Infections caused by coagulase-negative staphylococci generally resolve with antimicrobial therapy alone. Indwelling Foley catheters can also predispose to infections in these patients, and change or removal of the catheter should be considered for persistent urinary infections.

If cultures are positive, antibiotic therapy is adjusted to the results of sensitivity tests. If a patient defervesces within 72 h, antibiotics are continued for at least 7 days and until the patient has no symptoms or signs of infection. When neutropenia is transient (such as that following myelosuppressive chemotherapy), antibiotic therapy is usually continued until the neutrophil count is > 500/µL; however, stopping antimicrobials can be considered in selected patients with persistent neutropenia, especially those in whom symptoms and signs of inflammation have resolved, if cultures remain negative.

Fever that persists > 72 h despite antibiotic therapy suggests a nonbacterial cause, infection with a resistant species, a superinfection with a 2nd bacterial species, inadequate serum or tissue levels of the antibiotics, or localized infection, such as an abscess. Neutropenic patients with persistent fever are reassessed every 2 to 4 days with physical examination, cultures, and chest x-ray. If the patient is well except for the presence of fever, the initial antibiotic regimen can be continued. If the patient is deteriorating, alteration of the antimicrobial regimen is considered.

Fungal infections are the most likely cause of persistent fevers and deterioration. Antifungal therapy (eg, with azole, echinocandin, or polyene drug) is added empirically if unexplained fever persists after 4 days of broad-spectrum antibiotic therapy. If fever persists after 3 wk of empiric therapy (including 2 wk of antifungal therapy) and the neutropenia has resolved, then stopping all antimicrobials is considered and the cause of fever reevaluated.

Antibiotic prophylaxis in afebrile neutropenic patients remains controversial. Trimethoprim/sulfamethoxazole (TMP/SMX) prevents *Pneumocystis jirovecii* pneumonia in neutropenic and nonneutropenic patients with associated impaired cell-mediated immunity. Also, TMP/SMX may prevent bacterial infections in patients expected to be profoundly neutropenic for > 1 wk. The disadvantages of TMP/SMX prophylaxis include adverse effects, potential myelosuppression, and development of resistant bacteria and oral candidiasis. Antifungal prophylaxis is not routinely recommended for neutropenic patients, but patients at high risk of developing fungal infections (eg, after bone marrow transplantation and after receiving high doses of corticosteroids) may benefit.

Myeloid growth factors (granulocyte-macrophage colony-stimulating factor [GM-CSF] and granulocyte colony-stimulating factor [G-CSF]) are now widely used to increase the neutrophil count and to prevent infections in patients with severe neutropenia (eg, after bone marrow transplantation and intensive cancer chemotherapy). They are expensive. However, if the risk of febrile neutropenia is ≥ 30% (as assessed by neutrophil count < 500 µL, presence of infection during a previous cycle of chemotherapy, associated comorbid disease, or age > 75), growth factors are indicated. In general, most clinical benefit occurs when the growth factor is administered beginning about 24 h after completion of chemotherapy. Patients with neutropenia caused by an idiosyncratic drug reaction may also benefit from myeloid growth factors, particularly if a delayed recovery is anticipated. The dose for G-CSF is 5 µg/kg sc once/day; for GM-CSF, 250 $\mu g/m^2$ sc once/day.

Glucocorticoids, anabolic steroids, and vitamins do not stimulate neutrophil production but can affect distribution and destruction. If acute neutropenia is suspected to be drug or toxin induced, all potentially etiologic agents are stopped. If neutropenia develops during treatment with a drug known to induce low counts (eg, chloramphenicol), then switching to an alternative antibiotic may be helpful.

Saline or hydrogen peroxide gargles every few hours, anesthetic lozenges (benzocaine 15 mg q 3 or 4 h), or chlorhexidine mouth rinses (1% solution) bid or tid may relieve the discomfort of stomatitis with oropharyngeal ulcerations. Oral or esophageal candidiasis is treated with nystatin (400,000 to 600,000 units oral rinse qid; swallowed if esophagitis is present) or with systemic antifungal drugs (eg,

fluconazole). A semisolid or liquid diet may be necessary during acute stomatitis or esophagitis to minimize discomfort.

Chronic neutropenia: Neutrophil production in congenital, cyclic, and idiopathic neutropenia can be increased with administration of G-CSF 1 to 10 µg/kg sc once/day. Effectiveness can be maintained with daily or intermittent G-CSF for months or years. Long-term G-CSF has also been used in other patients with chronic neutropenia, including those with myelodysplasia, HIV, and autoimmune disorders. In general, neutrophil counts increase, although clinical benefits are less clear, especially for patients who do not have severe neutropenia. For patients with autoimmune disorders or who have had an organ transplant, cyclosporine can also be beneficial.

In some patients with accelerated neutrophil destruction caused by autoimmune disorders, corticosteroids (generally, prednisone 0.5 to 1.0 mg/kg po once/day) increase blood neutrophils. This increase often can be maintained with alternate-day G-CSF therapy.

Splenectomy increases the neutrophil count in some patients with splenomegaly and splenic sequestration of neutrophils (eg, Felty's syndrome, hairy cell leukemia). However, splenectomy should be reserved for patients with severe neutropenia (ie, < 500/µL) and serious problems with infections in whom other treatments have failed. Patients should be vaccinated against infections caused by *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* before and after splenectomy because splenectomy predisposes patients to infection by encapsulated organisms.

Lymphocytopenia

Lymphocytopenia is a total lymphocyte count of < 1000/µL in adults or < 3000/µL in children < 2 yr. Sequelae include opportunistic infections and an increased risk of malignant and autoimmune disorders. If the CBC reveals lymphocytopenia, testing for immunodeficiency and analysis of lymphocyte subpopulations should follow. Treatment is directed at the underlying disorder.

The normal lymphocyte count in adults is 1000 to 4800/µL; in children < 2 yr, 3000 to 9500/µL. At age 6 yr, the lower limit of normal is 1500/µL. Both B and T cells are present in the peripheral blood; about 75% of the lymphocytes are T cells and 25% B cells. Because lymphocytes account for only 20 to 40% of the total WBC count, lymphocytopenia may go unnoticed when WBC count is checked without a differential.

Almost 65% of blood T cells are CD4+ (helper) T cells. Most patients with lymphocytopenia have a reduced absolute number of T cells, particularly in the number of CD4+ T cells. The average number of CD4+ T cells in adult blood is 1100/µL (range, 300 to 1300/µL), and the average number of cells of the other major T-cell subgroup, CD8+ (suppressor) T cells, is 600/µL (range, 100 to 900/µL).

Etiology

Lymphocytopenia can be acquired or inherited.

Acquired lymphocytopenia can occur with a number of other disorders (see Table 107-2). The most common causes include

• Protein-energy undernutrition

• AIDS

Protein-energy undernutrition is the most common cause worldwide. AIDS is the most common infectious disease causing lymphocytopenia, which arises from destruction of CD4+ T cells infected with HIV. Lymphocytopenia may also reflect impaired lymphocyte production arising from destruction of thymic or lymphoid architecture. In acute viremia due to HIV or other viruses, lymphocytes may undergo accelerated destruction from active infections with the virus, may be trapped in the spleen or lymph nodes, or may migrate to the respiratory tract.

Inherited lymphocytopenia (see Table 107-2) most commonly results from

• Severe combined immunodeficiency disorder

• Wiskott-Aldrich syndrome

It may occur with inherited immunodeficiency disorders (see Ch. 126) and disorders that involve impaired lymphocyte production. Other inherited disorders, such as Wiskott-Aldrich syndrome, adenosine deaminase deficiency, and purine nucleoside phosphorylase deficiency, may involve accelerated T-cell destruction. In many disorders, antibody production is also deficient.

Iatrogenic lymphocytopenia is caused by cytotoxic chemotherapy, radiation therapy, or the administration of antilymphocyte globulin (or other lymphocyte antibodies). Long-term treatment for psoriasis using psoralen and ultraviolet irradiation may destroy T cells. Glucocorticoids can induce lymphocyte destruction.

Lymphocytopenia may occur with autoimmune diseases such as SLE, RA, myasthenia gravis, and protein-losing enteropathy.

Symptoms and Signs

Lymphocytopenia per se generally causes no symptoms. However, findings of an associated disorder may include absent or diminished

[**Table 107-2.** Causes of Lymphocytopenia]

tonsils or lymph nodes, indicative of cellular immunodeficiency; skin abnormalities, such as alopecia, eczema, pyoderma, or telangiectasia; evidence of hematologic disease, such as pallor, petechiae, jaundice, or mouth ulcers; and generalized lymphadenopathy and splenomegaly, which may suggest HIV infection.

Lymphocytopenic patients experience recurrent infections or develop infections with unusual organisms. *Pneumocystis jirovecii*, cytomegalovirus, rubeola, and varicella pneumonias often are fatal. Lymphocytopenia is also a risk factor for cancer and for autoimmune disorders.

Diagnosis

• Clinical suspicion (repeated or unusual infections)

• CBC with differential

• Measurement of lymphocyte subpopulations and immunoglobulin levels

Lymphocytopenia is suspected in patients with recurrent viral, fungal, or parasitic infections but is usually detected incidentally on a CBC. *P. jirovecii*, cytomegalovirus, rubeola, or varicella pneumonias with lymphocytopenia suggest immunodeficiency. Lymphocyte subpopulations are measured in lymphocytopenic patients. Measurements of immunoglobulin levels should also be done to evaluate antibody production. Patients with a history of recurrent infections undergo complete laboratory evaluation for immunodeficiency (see p. 1095), even if initial screening tests are normal.

Treatment

• Treatment of underlying disorder

• Sometimes IV immune globulin

• Possibly stem cell transplantation

Lymphocytopenia usually remits with removal of the underlying factor or successful treatment of the underlying disorder in the acquired lymphocytopenias. Intravenous immune globulin is indicated if patients have chronic IgG deficiency, lymphocytopenia, and recurrent infections. Hematopoietic stem cell transplantation can be considered for all patients with congenital immunodeficiencies and may be curative (see p. 1132).

Chapter 108. Thrombocytopenia and Platelet Dysfunction

Introduction

Platelets are cell fragments that function in the clotting system. Thrombopoietin, primarily produced in the liver in response to decreased numbers of bone marrow megakaryocytes and circulating platelets, stimulates the bone marrow to synthesize platelets from megakaryocytes. Platelets circulate for 7 to 10 days. About one third are always transiently sequestered in the spleen. The platelet count is normally 140,000 to 440,000/µL. However, the count can vary slightly according to menstrual cycle phase, decrease during near-term pregnancy (gestational thrombocytopenia), and increase in response to inflammatory cytokines (secondary, or reactive, thrombocytosis). Platelets are eventually destroyed, primarily by the spleen.

Platelet disorders include

• An abnormal increase in platelets (thrombocythemia, a myeloproliferative disorder—see p. 997)

• A decrease in platelets (thrombocytopenia)

• Platelet dysfunction

Any of these conditions, even those in which platelets are increased, may cause defective formation of hemostatic plugs and bleeding.

The risk of bleeding is inversely proportional to the platelet count. When the platelet count is < 50,000/µL, minor bleeding occurs easily and the risk of major bleeding increases. Counts between 20,000 and 50,000/µL predispose to bleeding with trauma, even minor trauma; with counts < 20,000/µL, spontaneous bleeding may occur; with counts < 5000/µL, severe spontaneous bleeding is more likely. However, patients with counts < 10,000/µL may be asymptomatic for years.

Etiology

Thrombocytopenia: Causes of thrombocytopenia can be classified by mechanism (see Table 108-1) and include failed platelet production, increased splenic sequestration of platelets with normal platelet survival, increased platelet destruction or consumption (both immunologic and nonimmunologic causes), dilution of platelets, and a combination of these mechanisms.

[**Table 108-1.** Classification of Thrombocytopenia]

Increased splenic sequestration is suggested by splenomegaly.

A large number of drugs may cause thrombocytopenia (see p. 960), typically by triggering immunologic destruction.

Overall, the most common specific causes of thrombocytopenia include

• Gestational thrombocytopenia

• Drug-induced thrombocytopenia due to immune-mediated platelet destruction (commonly quinine, trimethoprim/sulfamethoxazole)

• Drug-induced thrombocytopenia due to dose-dependent bone marrow suppression (by chemotherapeutic agents)

• Thrombocytopenia accompanying systemic infection

• Immune thrombocytopenic purpura (ITP)

Platelet dysfunction: Platelet dysfunction may stem from an intrinsic platelet defect or from an extrinsic factor that alters the function of normal platelets. Dysfunction may be hereditary or acquired. Hereditary disorders of platelet function consist of von Willebrand's disease, the most common hereditary hemorrhagic disease, and hereditary intrinsic platelet disorders (see p. 957), which are much less common. Acquired disorders of platelet function (see p. 957) are commonly due to diseases as well as to aspirin and other drugs.

Symptoms and Signs

Platelet disorders result in a typical pattern of bleeding:

• Multiple petechiae in the skin (typically most evident on the lower legs)

• Scattered small ecchymoses at sites of minor trauma

• Mucosal bleeding (epistaxis, bleeding in the GI and GU tracts, vaginal bleeding)

• Excessive bleeding after surgery

Heavy GI bleeding and bleeding into the CNS may be life threatening. However, bleeding into tissues (eg, deep visceral hematomas or hemarthroses) does not occur with thrombocytopenia, which causes immediate, superficial bleeding; tissue bleeding (often delayed for up to a day after trauma) suggests a coagulation disorder (eg, hemophilia).

Diagnosis

• Clinical presentation of petechiae and mucosal bleeding

• CBC with platelets, coagulation studies, peripheral blood smear

• Sometimes bone marrow aspiration

• Sometimes von Willebrand's antigen and factor activity studies

Platelet disorders are suspected in patients with petechiae and mucosal bleeding. A CBC with platelet count, coagulation studies, and a peripheral blood smear are obtained. Excessive platelets and thrombocytopenia are diagnosed from the platelet count; coagulation studies are normal unless there is a simultaneous coagulopathy. In patients with a normal CBC, platelet count, and INR and normal or only slightly prolonged PTT, platelet dysfunction is suspected.

Thrombocytopenia: In patients with thrombocytopenia, the peripheral smear may suggest the cause (see Table 108-2). If the smear shows abnormalities other than thrombocytopenia, such as nucleated RBCs or abnormal or immature WBCs, bone marrow aspiration is indicated. Bone marrow aspiration reveals the number and appearance of megakaryocytes and is the definitive test for many disorders causing marrow failure. However, normal number and appearance of megakaryocytes does not always indicate normal platelet production. For example, in patients with immune thrombocytopenic purpura, platelet production is frequently decreased, or not appropriately increased, despite the normal appearance of megakaryocytes. If the bone marrow is normal but the spleen is enlarged, increased splenic sequestration is the likely cause of thrombocytopenia; if the bone marrow is normal and the spleen is not enlarged, excess platelet destruction is the likely cause. Measurement of antiplatelet antibodies is not clinically useful. HIV testing is done in patients at risk of HIV infection.

Suspected platelet dysfunction: In patients with platelet dysfunction, a drug cause is suspected if symptoms began only after patients started taking a potentially causative drug. A hereditary cause is suspected if there is a lifelong history of easy bruising and bleeding after tooth extractions or surgery. In the case of a suspected hereditary cause, von Willebrand's antigen and factor activity studies are obtained. Platelet dysfunction caused by systemic disorders is typically mild and of minor clinical

importance. In these patients, the causative systemic disorder is the clinical concern, and hematologic tests are unnecessary.

[Table 108-2. Peripheral Blood Findings in Thrombocytopenic Disorders]

Treatment

• Avoidance of drugs that impair platelet function

• Rarely platelet transfusions

In patients with thrombocytopenia or platelet dysfunction, drugs that further impair platelet function, particularly aspirin and other NSAIDs, should not be given. Patients who are already taking such drugs should consider alternative drugs, such as acetaminophen, or simply stop using them.

Patients may require platelet transfusion, but transfusions are given only in limited situations (see p. 1039). Prophylactic transfusions are used sparingly because they may lose their effectiveness with repeated use due to the development of platelet alloantibodies. In platelet dysfunction or thrombocytopenia caused by decreased production, transfusions are reserved for patients with active bleeding or severe thrombocytopenia (eg, platelet count < 10,000/µL). In thrombocytopenia caused by platelet destruction, transfusions are reserved for life-threatening or CNS bleeding.

Acquired Platelet Dysfunction

Acquired platelet dysfunction, which is common, may result from aspirin, other NSAIDs, or systemic disorders.

Acquired abnormalities of platelet function are very common. Causes include

• Drugs

• Systemic disorders

• Cardiopulmonary bypass

Acquired platelet dysfunction is suspected and diagnosed when an isolated prolongation of bleeding time is observed and other possible diagnoses have been eliminated. Platelet aggregation studies are unnecessary.

Drugs: Aspirin and other NSAIDs, which are very commonly used drugs, may induce platelet dysfunction. Sometimes this effect is incidental (eg, when the drugs are used to relieve pain and inflammation) and sometimes therapeutic (eg, when aspirin is used for prevention of stroke or coronary thrombosis). Other therapeutic antiplatelet drugs include clopidogrel, ticlopidine, and the glycoprotein IIb/IIIa inhibitors.

Aspirin and NSAIDs prevent cyclooxygenase-mediated production of thromboxane A_2. This effect can last 5 to 7 days. Aspirin modestly prolongs bleeding time in healthy people but may markedly prolong bleeding time in patients with underlying platelet dysfunction or a severe coagulation disturbance (eg, patients receiving heparin, patients with severe hemophilia).

Systemic disorders: Many disorders (eg, myeloproliferative and myelodysplastic disorders, uremia, macroglobulinemia and multiple myeloma, cirrhosis, SLE) can impair platelet function.

Uremia may prolong bleeding via unknown mechanisms. If bleeding is observed clinically, bleeding time may be corrected transiently with vigorous dialysis, cryoprecipitate administration, or desmopressin infusion. If indicated for treatment of anemia, RBC count can be increased by transfusion or by giving erythropoietin; this process also shortens the bleeding time.

Cardiopulmonary bypass: Platelets may become dysfunctional, prolonging the bleeding time as blood

circulates through a pump oxygenator during cardiopulmonary bypass. The mechanism appears to be activation of fibrinolysis on the platelet surface with resultant loss of the glycoprotein Ib-IX binding site for von Willebrand's factor. Regardless of platelet count, patients who bleed excessively after cardiopulmonary bypass and who have a long bleeding time are transfused with platelets. Giving aprotinin (a protease inhibitor that neutralizes plasmin activity) during bypass may preserve platelet function, prevent prolongation of bleeding time, and reduce the need for transfusion.

Hereditary Intrinsic Platelet Disorders

Hereditary intrinsic platelet disorders are rare and produce lifelong bleeding tendencies. Diagnosis is confirmed by platelet aggregation tests. Platelet transfusion is necessary to control serious bleeding.

Normal hemostasis requires platelet adhesion and activation.

Adhesion (ie, of platelets to exposed vascular subendothelium) requires von Willebrand's factor (VWF) and the platelet glycoprotein Ib-IX complex.

Activation promotes platelet aggregation and fibrinogen binding and requires the platelet glycoprotein IIb-IIIa complex. Activation involves release of adenosine diphosphate (ADP) from platelet storage granules and conversion of arachidonic acid to thromboxane A_2 via a cyclooxygenase-mediated reaction.

Hereditary intrinsic platelet disorders can involve defects in any of these substrates and steps. These disorders are suspected in patients with lifelong bleeding disorders who have normal platelet counts and coagulation study results. Diagnosis usually is based on platelet aggregation tests; however, platelet aggregation tests are not quantitative, and interpretation of results is often inconclusive (see Table 108-3).

Disorders of adhesion: Bernard-Soulier syndrome is a rare autosomal recessive disorder. It impairs platelet adhesion via a defect in the glycoprotein Ib-IX complex. Bleeding may be severe. Platelets are unusually large. They do not aggregate with ristocetin but aggregate normally with ADP, collagen, and epinephrine.

Large platelets associated with functional abnormalities also occur in the May-Hegglin anomaly, a thrombocytopenic disorder with abnormal WBCs, and in the Chediak-Higashi syndrome (see p. 1101).

Platelet transfusion is necessary to control serious bleeding.

Disorders of activation: Disorders of amplification of platelet activation are the most common hereditary intrinsic platelet disorders and produce mild bleeding. They may result from decreased ADP in the platelet granules (storage pool deficiency), from an inability to generate thromboxane A_2 from arachidonic acid, or from an inability of platelets to aggregate in response to thromboxane A_2. Platelet aggregation tests reveal impaired aggregation after exposure to collagen, epinephrine, and low levels of ADP and normal aggregation after exposure to high levels of ADP. The same pattern can result from use of NSAIDs or aspirin, the effect of which can persist for several days. Therefore, platelet aggregation tests should not be done in patients who have recently taken these drugs.

Thrombasthenia (Glanzmann disease) is a rare autosomal recessive disorder causing a defect in the platelet glycoprotein IIb-IIIa complex; platelets cannot aggregate. Patients may experience severe mucosal bleeding (eg, nosebleeds that stop only after nasal packing and transfusions of platelet concentrates). The diagnosis is suggested by a finding of single platelets without aggregates on a peripheral blood smear obtained from a finger stick. It is confirmed by the finding that platelets fail to aggregate with epinephrine, collagen, or even high levels of ADP but do aggregate transiently with ristocetin. Platelet transfusion is necessary to control serious bleeding.

Immune Thrombocytopenic Purpura

(Idiopathic Thrombocytopenic Purpura)

Immune thrombocytopenic purpura (ITP) is a bleeding disorder caused by thrombocytopenia not associated with a systemic disease. Typically, it is chronic in adults but is usually acute and self-limited in children. Spleen size is normal. Diagnosis requires that other disorders be excluded through selective tests. Treatment includes corticosteroids, splenectomy, and immunosuppressants and thrombopoietic-mimetic drugs. For life-threatening bleeding, platelet transfusions, IV corticosteroids, and IV immune globulin are required.

ITP usually results from development of an autoantibody directed against a structural platelet antigen. In childhood ITP, the autoantibody may be triggered by binding of viral antigen to megakaryocytes.

Symptoms and Signs

The symptoms and signs are petechiae, purpura, and mucosal bleeding. Gross GI bleeding and hematuria are uncommon. The

[Table 108-3. Results of Aggregation Tests in Hereditary Disorders of Platelet Function]

spleen is of normal size unless it is enlarged by a coexisting childhood viral infection.

Diagnosis

• CBC with platelets, peripheral blood smear

• Sometimes bone marrow aspiration

• Exclusion of other thrombocytopenic disorders

ITP is suspected in patients with isolated thrombocytopenia (ie, otherwise normal CBC and peripheral blood smear). Because manifestations of ITP are nonspecific, other causes of isolated thrombocytopenia (eg, drugs, alcohol, lymphoproliferative disorders, systemic illness) need to be excluded by clinical evaluation and appropriate testing. Typically, patients have coagulation studies, liver function tests (including testing for hepatitis C), and, because HIV-associated thrombocytopenia may be otherwise indistinguishable from ITP, HIV testing. Testing for antiplatelet antibodies does not aid diagnosis or treatment.

Bone marrow examination is not required to make the diagnosis but is done if blood counts or blood smear reveals abnormalities in addition to thrombocytopenia, when clinical features are not typical, and in patients > 60 yr (because myelodysplasia is more common in older patients). In patients with ITP, bone marrow examination reveals normal or possibly increased numbers of megakaryocytes in an otherwise normal bone marrow sample.

Prognosis

Children typically recover spontaneously, even from severe thrombocytopenia, in several weeks to months.

In adults, spontaneous remission is rare. However, some have mild and stable disease (ie, platelet counts > 30,000/µL); such cases may be more common than previously thought, many being discovered by the automated platelet counting now routinely done with CBC. Others have significant, symptomatic thrombocytopenia, although life-threatening bleeding and death are rare.

Treatment

• Oral corticosteroids

• Splenectomy

• Rituximab

• Sometimes thrombopoietic-mimetic drugs

• Sometimes other immunosuppressants

• For severe bleeding, IV immune globulin, IV corticosteroids, or platelet transfusions

Adults usually are given an oral corticosteroid (eg, prednisone 1 mg/kg once/day) initially. In patients who respond, the platelet count rises to normal within 2 to 6 wk. The corticosteroid dosage is then tapered. An alternative corticosteroid regimen is dexamethasone 40 mg po once/day for 4 days. However, most patients do not respond adequately or relapse as the corticosteroid is tapered. Splenectomy can achieve a complete remission in about two thirds of these patients but is usually reserved for those with severe thrombocytopenia, bleeding, or both; it may not be appropriate for those with mild disease. Rituximab (375 mg/m^2 IV once/wk for 4 wk) may be used in patients who do not respond to splenectomy or in patients who are not candidates for splenectomy.

Because other treatments may not be effective for patients with ITP refractory to corticosteroids and splenectomy and because ITP often has a benign natural history, additional treatments may not be indicated unless the platelet count is < 10,000 to 20,000/µL and active bleeding is present. In these patients, thrombopoietin-mimetic drugs, such as romiplostim 1 to 5 µg/kg sc once/wk and eltrombopag 50 to 75 mg po once/day, may be used.

About 75 to 80% of patients respond to thrombopoietin-mimetic drugs even after failure of multiple previous treatments. However, these drugs are used for maintenance therapy rather than induction of remission and need to be administered continuously to maintain the platelet count > 50,000/µL. More intensive immunosuppression may be required with drugs such as cyclophosphamide and azathioprine in patients unresponsive to other drugs who have severe, symptomatic thrombocytopenia.

Treatment of children is usually supportive, because most children spontaneously recover. Even after months or years of thrombocytopenia, most children have spontaneous remissions. If mucosal bleeding occurs, corticosteroids or IV immune globulin is given. Initial use of corticosteroids and IV immune globulin is controversial, because they increase platelet count but may not improve clinical outcome. Splenectomy is rarely done in children. However, if thrombocytopenia is severe and symptomatic for > 6 mo, then splenectomy is effective.

In children or adults with ITP and life-threatening bleeding, rapid phagocytic blockade is attempted by giving IV immune globulin 1 g/kg once/day for 1 to 2 days. This treatment usually causes the platelet count to rise within 2 to 4 days, but the count remains high only for 2 to 4 wk. High-dose methylprednisolone (1 g IV once/day for 3 days) is less expensive than IV immune globulin and is easier to administer but may not be as effective. Patients with ITP and life-threatening bleeding are also given platelet transfusions. Platelet transfusions are not used prophylactically.

Oral corticosteroids or IV immune globulin may also be given when a transient increase of the platelet count is required for tooth extractions, childbirth, surgery, or other invasive procedures.

Thrombocytopenia Due to Splenic Sequestration

Increased splenic platelet sequestration can occur in various disorders that cause splenomegaly. Sequestration is expected in patients with congestive splenomegaly caused by advanced cirrhosis. The platelet count usually is > 30,000/µL unless the disorder causing the splenomegaly also impairs platelet production (eg, in myelofibrosis with myeloid metaplasia). Platelets are released from the spleen by epinephrine and therefore may be available at a time of stress. Therefore, thrombocytopenia caused only by splenic sequestration does not cause bleeding. Splenectomy corrects the thrombocytopenia but is not indicated unless severe thrombocytopenia from simultaneous marrow failure is present.

Thrombocytopenia: Other Causes

Platelet destruction can develop because of immunologic causes (HIV infection, drugs, connective tissue or lymphoproliferative disorders, blood transfusions) or nonimmunologic causes (sepsis, acute respiratory distress syndrome). Manifestations are petechiae, purpura, and mucosal bleeding. Laboratory findings depend on the cause. The history may be the only suggestion of the diagnosis. Treatment is correction of the underlying disorder.

Acute respiratory distress syndrome: Patients with acute respiratory distress syndrome may develop nonimmunologic thrombocytopenia, possibly secondary to deposition of platelets in the pulmonary capillary bed.

Blood transfusions: Posttransfusion purpura causes immunologic platelet destruction indistinguishable from immune thrombocytopenic purpura (ITP), except for a history of a blood transfusion within the preceding 7 to 10 days. The patient, usually a woman, lacks a platelet antigen (PLA-1) present in most people. Transfusion with PLA-1-positive platelets stimulates formation of anti-PLA-1 antibodies, which (by an unknown mechanism) can react with the patient's PLA-1-negative platelets. Severe thrombocytopenia results, taking 2 to 6 wk to subside.

Connective tissue and lymphoproliferative disorders: Connective tissue (eg, SLE) or lymphoproliferative disorders can cause immunologic thrombocytopenia. Corticosteroids and splenectomy are often effective.

Drug-induced immunologic destruction: Commonly used drugs that occasionally induce thrombocytopenia include

• Quinine

• Trimethoprim/sulfamethoxazole

• Glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban)

• Hydrochlorothiazide

• Carbamazepine

• Acetaminophen

• Chlorpropamide

• Ranitidine

• Rifampin

• Vancomycin

Drug-induced thrombocytopenia occurs typically by causing an immune reaction in which drug bound to the platelet creates a new and "foreign" antigen. This disorder is indistinguishable from ITP except for the history of drug ingestion. When the drug is stopped, the platelet count typically begins to increase within 1 to 2 days and recovers to normal within 7 days.

Up to 5% of patients receiving unfractionated heparin develop thrombocytopenia, which may occur even with very-low-dose heparin (eg, used in flushes to keep IV or arterial lines open). The mechanism is usually immunologic. Bleeding can occur, but more commonly platelets clump excessively, causing vessel obstruction, leading to paradoxical arterial and venous thromboses, which may be life threatening (eg, thromboembolic occlusion of limb arteries, stroke, acute MI). Heparin should be stopped in any patient who becomes thrombocytopenic or whose platelet count decreases by more than 50%. Because 5 days of heparin is sufficient to treat venous thrombosis and because most patients begin oral anticoagulants simultaneously with heparin, stopping heparin is usually safe. Low mol wt heparin (LMWH) may be less

immunogenic than unfractionated heparin. However, LMWH is not useful if heparin-induced thrombocytopenia has already developed, because most antibodies cross-react with LMWH.

Infections: HIV infection may cause immunologic thrombocytopenia indistinguishable from ITP except for the association with HIV. The platelet count may increase with glucocorticoids, which are often withheld unless the platelet count falls to < 20,000/µL, because these drugs may further depress immune function. The platelet count also usually increases after treatment with antiviral drugs.

Other infections such as systemic viral infections (eg, Epstein-Barr virus, cytomegalovirus), rickettsial infections (eg, Rocky Mountain spotted fever), and bacterial sepsis are typically associated with thrombocytopenia.

Pregnancy: Mild thrombocytopenia, typically asymptomatic, occurs late in gestation in about 5% of normal pregnancies (gestational thrombocytopenia); it is usually mild (platelet counts < 70,000/µL are rare), requires no treatment, and resolves after delivery. However, severe thrombocytopenia may develop in pregnant women with preeclampsia and the HELLP syndrome (hemolysis, elevated liver function tests, and low platelets—see p. 2670); such women typically require immediate delivery, and platelet transfusion is considered if platelet count is < 20,000/µL (or < 50,000/L if delivery is to be cesarean).

Sepsis: Sepsis often causes nonimmunologic thrombocytopenia that parallels the severity of the infection. The thrombocytopenia has multiple causes: disseminated intravascular coagulation, formation of immune complexes that can associate with platelets, activation of complement, and deposition of platelets on damaged endothelial surfaces.

Thrombotic Thrombocytopenic Purpura and Hemolytic-Uremic Syndrome

Thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS) are acute, fulminant disorders characterized by thrombocytopenia and microangiopathic hemolytic anemia. Other manifestations may include alterations in level of consciousness and renal failure. Diagnosis requires demonstrating characteristic laboratory test abnormalities, including Coombs'-negative hemolytic anemia. Treatment is plasma exchange and corticosteroids in adults and supportive care (sometimes including hemodialysis) in children.

Pathophysiology

TTP and HUS involve nonimmunologic platelet destruction. Loose strands of von Willebrand's factor (VWF) or fibrin are deposited in multiple small vessels and damage passing platelets and RBCs, causing significant thrombocytopenia and anemia. Platelets are also destroyed within multiple small thrombi. Multiple organs develop bland platelet-VWF thrombi (without the vessel wall granulocytic infiltration characteristic of vasculitis) localized primarily to arteriocapillary junctions, described as thrombotic microangiopathy. The brain, heart, and kidneys are particularly likely to be affected.

TTP and HUS differ mainly in the relative degree of renal failure. Typically, disorders in adults are described as TTP and are less likely to involve renal failure. HUS is used to describe the disorder in children, which typically involves renal failure.

Etiology

Children: Most cases follow acute hemorrhagic colitis resulting from *Shiga* toxin-producing bacteria (eg, *Escherichia coli* O157:H7, some strains of *Shigella dysenteriae*).

Adults: Many cases are idiopathic. Known causes and associations include

- Drugs: Quinine (most common), immunosuppressants, and cancer chemotherapy drugs (eg, cyclosporine, mitomycin C)

- Pregnancy (often indistinguishable from severe preeclampsia or eclampsia)

• Rarely, hemorrhagic colitis due to *Escherichia coli* O157:H7

A predisposing factor in many patients is congenital or acquired deficiency of the plasma enzyme ADAMTS13, which cleaves VWF and thus eliminates abnormally large VWF multimers that can cause platelet thrombi.

Symptoms and Signs

Manifestations of ischemia develop with varying severity in multiple organs. These manifestations include weakness, confusion and coma, abdominal pain, nausea, vomiting, diarrhea, and arrhythmias caused by myocardial damage. Children usually have a prodrome of vomiting, abdominal pain, and diarrhea (frequently bloody). Fever may occur, but high fever with chills does not occur in TTP or HUS and suggests sepsis. The clinical syndromes of TTP and HUS are indistinguishable, except that neurologic symptoms are less common with HUS.

Diagnosis

• CBC with platelets, peripheral blood smear, Coombs' test

• Exclusion of other thrombocytopenic disorders

TTP-HUS is suspected in patients with suggestive symptoms, thrombocytopenia, and anemia. If the disorder is suspected, urinalysis, peripheral blood smear, reticulocyte count, serum LDH, renal function tests, serum bilirubin (direct and indirect), and Coombs' test are done. The diagnosis is suggested by:

• Thrombocytopenia and anemia

• Fragmented RBCs on the blood smear (helmet cells, triangular RBCs, distorted-appearing RBCs; these changes describe microangiopathic hemolysis)

• Evidence of hemolysis (falling Hb level, polychromasia, elevated reticulocyte count, elevated serum LDH)

• Negative direct antiglobulin (Coombs') test

Otherwise unexplained thrombocytopenia and microangiopathic hemolytic anemia are sufficient evidence for a presumptive diagnosis.

Causes: Although causes (eg, quinine sensitivity) or associations (eg, pregnancy) are clear in some patients, in most patients TTP-HUS appears suddenly and spontaneously without apparent cause. TTP-HUS is often indistinguishable, even with renal biopsy, from syndromes that cause identical thrombotic microangiopathies (eg, preeclampsia, systemic sclerosis, accelerated hypertension, acute renal allograft rejection).

Testing for ADAMTS13 activity is appropriate in patients with suspected TTP-HUS, except in children who have typical diarrhea-associated HUS. Although the results of ADAMTS13 testing do not affect initial treatment, results are important prognostically.

Stool testing (specific culture for *E. coli* O157:H7 or *Shiga* toxin assay) is done in children with diarrhea and also adults who had a prodrome of bloody diarrhea; however, the organism and toxin may have cleared by the time of presentation.

Treatment

• Plasma exchange and corticosteroids in adults

Typical diarrhea-associated HUS in children caused by enterohemorrhagic infection usually spontaneously remits and is treated with supportive care and not plasma exchange; over half of patients

require renal dialysis. In other cases, untreated TTP-HUS is almost always fatal. With plasma exchange, however, > 85% of patients recover completely.

Plasma exchange is continued daily until evidence of disease activity has subsided, as indicated by a normal platelet count, which may be several days to many weeks. Adults with TTP are also given corticosteroids. In patients with recurrence when plasma exchange is stopped or in patients with relapses, more intensive immunosuppression with rituximab may be effective. Most patients experience only a single episode of TTP-HUS. However, relapses occur in about 40% of patients who have a severe deficiency of ADAMTS13 activity caused by an autoantibody inhibitor. Patients must be evaluated quickly if symptoms suggestive of a relapse develop.

Von Willebrand's Disease

Von Willebrand's disease (VWD) is a hereditary deficiency of von Willebrand's factor (VWF), which causes platelet dysfunction. Bleeding tendency is usually mild. Screening tests show a normal platelet count and, possibly, a slightly prolonged PTT. Diagnosis is based on low levels of VWF antigen and abnormal ristocetin cofactor activity. Treatment involves control of bleeding with replacement therapy (cryoprecipitate or pasteurized intermediate-purity factor VIII concentrate) or desmopressin.

VWF is synthesized and secreted by vascular endothelium to form part of the perivascular matrix. VWF promotes the platelet adhesion phase of hemostasis by binding with a receptor on the platelet surface membrane (glycoprotein Ib/IX), which connects the platelets to the vessel wall. VWF is also required to maintain normal plasma factor VIII levels. Levels of VWF can temporarily increase in response to stress, exercise, pregnancy, inflammation, or infection.

VWD is classified into 3 types:

- Type 1: a quantitative deficiency of VWF, which is the most common form and is an autosomal dominant disorder

- Type 2: a qualitative impairment in synthesis of VWF that can result from various genetic abnormalities and is an autosomal dominant disorder

- Type 3: a rare autosomal recessive disorder in which homozygotes have no detectable VWF

Although VWD, like hemophilia A, is a hereditary disorder that may, when severe, cause factor VIII deficiency, the deficiency is usually only moderate.

Symptoms and Signs

Bleeding manifestations are mild to moderate and include easy bruising, mucosal bleeding, bleeding from small skin cuts that may stop and start over hours, sometimes increased menstrual bleeding, and abnormal bleeding after surgical procedures (eg, tooth extraction, tonsillectomy). Platelets function well enough that petechiae and purpura do not occur.

Diagnosis

- Total plasma VWF antigen, VWF function, and plasma factor VIII level

VWD is suspected in patients with bleeding disorders, particularly those with a family history of the disorder. Screening coagulation tests reveal a normal platelet count, normal INR, and sometimes a slightly prolonged PTT. Bleeding time may be prolonged, but this test has poor reproducibility and is of limited value. Diagnosis requires measuring total plasma VWF antigen, VWF function as determined by the ability of plasma to support agglutination of normal platelets by ristocetin (ristocetin cofactor activity), and plasma factor VIII level. Stimuli that temporarily increase VWF levels can cause false-negative results in mild VWD; tests may need to be repeated.

In the common (type 1) form of VWD, results are concordant; ie, VWF antigen, VWF function, and plasma factor VIII level are equally depressed. The degree of depression varies from about 15 to 60% of normal and determines the severity of a patient's abnormal bleeding. Levels of VWF antigen can also be as low as 40% of normal in healthy people with type O blood.

Type 2 variants are suspected if tests are discordant, ie, VWF antigen is higher than expected for the degree of abnormality in ristocetin cofactor activity. (VWF antigen is higher than expected because the VWF defect in type 2 is qualitative, not quantitative.) Diagnosis is confirmed by demonstrating a reduced concentration of large VWF multimers on agarose gel electrophoresis. Four different type 2 variants are recognized, distinguished by different functional abnormalities of the VWF molecule.

Patients with type 3 VWD have no detectable VWF and a marked deficiency of factor VIII.

Treatment

• VWF replacement when necessary

Patients are treated only if they are actively bleeding or are undergoing an invasive procedure (eg, surgery, dental extraction). Treatment involves replacement of VWF by infusion of pasteurized intermediate-purity factor VIII concentrates, which contain components of VWF. These concentrates are virally inactivated and therefore do not transmit HIV infection or hepatitis. Because they do not cause transfusion-transmitted infections, these concentrates are preferred to the previously used cryoprecipitate. High-purity factor VIII concentrates are prepared by immunoaffinity chromatography and contain no VWF.

Desmopressin is an analog of antidiuretic hormone (vasopressin) that stimulates release of VWF into the plasma and may increase levels of factor VIII. Desmopressin can be helpful for type 1 VWD but is usually of no value in other types and may even be harmful in some. To ensure adequate response to the drug, physicians give patients a test dose and measure the response of VWF antigen. Desmopressin 0.3 µg/kg given in 50 mL of 0.9% saline solution IV over 15 to 30 min may enable patients to undergo minor procedures (eg, tooth extraction, minor surgery) without needing replacement therapy. If a replacement product is needed, desmopressin may reduce the required dose. One dose of desmopressin is effective for about 8 to 10 h. About 48 h must elapse for new stores of VWF to accumulate, permitting a 2nd injection of desmopressin to be as effective as the initial dose.

Chapter 109. Hemostasis

Introduction

Hemostasis, the arrest of bleeding from an injured blood vessel, requires the combined activity of vascular, platelet, and plasma factors. Regulatory mechanisms counterbalance the tendency of clots to form. Hemostatic abnormalities can lead to excessive bleeding or thrombosis.

Vascular Factors

Vascular factors reduce blood loss from trauma through local vasoconstriction (an immediate reaction to injury) and compression of injured vessels by extravasation of blood into surrounding tissues. Vessel wall injury triggers the attachment and activation of platelets and production of fibrin; platelets and fibrin combine to form a clot.

Platelet Factors

Various mechanisms, including endothelial cell nitric oxide and prostacyclin, promote blood fluidity by preventing platelet stasis and dilating intact blood vessels. These mediators are no longer produced when the vascular endothelium is disrupted. Under these conditions, platelets adhere to the damaged intima and form aggregates. Initial platelet adhesion is to von Willebrand's factor (VWF), previously secreted by endothelial cells into the subendothelium. VWF binds to receptors on the platelet surface membrane (glycoprotein Ib/IX). Platelets anchored to the vessel wall undergo activation. During activation, platelets release mediators from storage granules, including adenosine diphosphate (ADP). Other biochemical changes resulting from activation include hydrolysis of membrane phospholipids, inhibition of adenylate cyclase, mobilization of intracellular Ca, and phosphorylation of intracellular proteins. Arachidonic acid is converted to thromboxane A_2; this reaction requires cyclooxygenase and is inhibited irreversibly by aspirin and reversibly by many NSAIDs. ADP, thromboxane A_2, and other mediators induce activation and aggregation of additional platelets on the injured endothelium. Another receptor is assembled on the platelet surface membrane from glycoproteins IIb and IIIa. Fibrinogen binds to the glycoprotein IIb/IIIa complexes of adjacent platelets, connecting them into aggregates.

Platelets provide surfaces for the assembly and activation of coagulation complexes and the generation of thrombin. Thrombin converts fibrinogen to fibrin. Fibrin strands bind aggregated platelets to help secure the platelet-fibrin hemostatic plug.

Plasma Factors

Plasma coagulation factors interact to produce thrombin, which converts fibrinogen to fibrin. Radiating from and anchoring the hemostatic plug, fibrin strengthens the clot.

In the intrinsic pathway, factor XII, high mol wt kininogen, prekallikrein, and activated factor XI (factor XIa) interact to produce factor IXa from factor IX. Factor IXa then combines with factor VIIIa and procoagulant phospholipid (present on the surface of activated platelets and tissue cells) to form a complex that activates factor X. In the extrinsic pathway, factor VIIa and tissue factor directly activate factor X (the factor VIIa/tissue factor complex also activates factor IX—see
Fig. 109-1 and
Table 109-1).

[**Fig. 109-1.** Pathways in blood coagulation.]

[**Table 109-1.** Components of Blood Coagulation Reactions]

Activation of the intrinsic or extrinsic pathway activates the common pathway, resulting in formation of the fibrin clot. Three steps are involved in common pathway activation:

1. A prothrombin activator is produced on the surface of activated platelets and tissue cells. The activator

is a complex of an enzyme, factor Xa, and 2 cofactors, factor Va and procoagulant phospholipid.

2. The prothrombin activator cleaves prothrombin into thrombin and another fragment.

3. Thrombin induces the generation of fibrin polymers from fibrinogen. Thrombin also activates factor XIII, an enzyme that catalyzes formation of stronger bonds between adjacent fibrin monomers, as well as factor VIII and factor XI.

Ca^{2+} ions are needed in most thrombin-generating reactions (Ca^{2+}-chelating agents [eg, citrate, ethylenediaminetetraacetic acid] are used in vitro as anticoagulants). Vitamin K-dependent clotting factors (factors II, VII, IX, and X) cannot bind normally to phospholipid surfaces through Ca^{2+} bridges and function in blood coagulation when synthesized in the absence of vitamin K.

Although the coagulation pathways are helpful in understanding mechanisms and laboratory evaluation of coagulation disorders, in vivo coagulation is predominantly via the extrinsic pathway. People with hereditary deficiencies of factor XII, high mol wt kininogen, or prekallikrein have no bleeding abnormality. People with hereditary factor XI deficiency have a mild to moderate bleeding disorder. In vivo, factor XI (an intrinsic pathway factor) is activated when a small amount of thrombin is generated. Factor IX can be activated both by factor XIa and factor VIIa/tissue factor complexes.

In vivo, initiation of the extrinsic pathway occurs when injury to blood vessels brings blood into contact with the tissue factor on membranes of cells within and around the vessel walls. This contact with tissue factor generates factor VIIa/tissue factor complexes that activate factor X and factor IX. Factor IXa, combined with its cofactor, factor VIIIa, on phospholipid membrane surfaces generates additional factor Xa. Factor X activation by both factor VIIa/tissue factor and factor IXa/VIIIa complexes is required for normal hemostasis. This requirement for factors VIII and IX explains why hemophilia type A (deficiency of factor VIII) or type B (deficiency of factor IX) results in bleeding, despite an intact extrinsic coagulation pathway initiated by factor VIIa/tissue factor complexes.

Regulatory Mechanisms

Several inhibitory mechanisms prevent activated coagulation reactions from amplifying uncontrollably, causing extensive local thrombosis or disseminated intravascular coagulation. These mechanisms include inactivation of procoagulant enzymes, fibrinolysis, and hepatic clearance of activated clotting factors.

Inactivation of coagulation factors: Plasma protease inhibitors (antithrombin, tissue factor pathway inhibitor, α_2-macroglobulin, heparin cofactor II) inactivate coagulation enzymes. Antithrombin inhibits thrombin, factor Xa, factor XIa, and factor IXa. Heparin enhances antithrombin activity.

Two vitamin K-dependent proteins, protein C and protein S, form a complex that inactivates factors VIIIa and Va by proteolysis. Thrombin, when bound to a receptor on endothelial cells (thrombomodulin), activates protein C. Activated protein C, in combination with protein S and phospholipid cofactors, proteolyzes and inactivates factors VIIIa and Va.

Fibrinolysis: Fibrin deposition and lysis must be balanced to maintain and remold the hemostatic seal during repair of an injured vessel wall. The fibrinolytic system dissolves fibrin by means of plasmin, a proteolytic enzyme. Fibrinolysis is activated by plasminogen activators released from vascular endothelial cells. Plasminogen activators and plasminogen (from plasma) bind to fibrin, and plasminogen activators cleave plasminogen into plasmin (see Fig. 109-2). Plasmin then proteolyzes fibrin into soluble fibrin degradation products that are swept away in the circulation.

There are several plasminogen activators:

• **Tissue plasminogen activator** (tPA), from endothelial cells, is a poor activator when

[**Fig. 109-2.** Fibrinolytic pathway.]

free in solution but an efficient activator when bound to fibrin in proximity to plasminogen.

- **Urokinase** exists in single-chain and double-chain forms with different functional properties. Single-chain urokinase cannot activate free plasminogen but, like tPA, can readily activate plasminogen bound to fibrin. A trace concentration of plasmin cleaves single-chain to double-chain urokinase, which activates plasminogen in solution as well as plasminogen bound to fibrin. Epithelial cells that line excretory passages (eg, renal tubules, mammary ducts) secrete urokinase, which is the physiologic activator of fibrinolysis in these channels.

- **Streptokinase**, a bacterial product not normally found in the body, is another potent plasminogen activator.

Streptokinase, urokinase, and recombinant tPA (alteplase) have all been used therapeutically to induce fibrinolysis in patients with acute thrombotic disorders.

Regulation of fibrinolysis: Fibrinolysis is regulated by plasminogen activator inhibitors (PAIs) and plasmin inhibitors that slow fibrinolysis. PAI-1, the most important PAI, inactivates tPA and urokinase and is released from vascular endothelial cells and activated platelets. The primary plasmin inhibitor is α_2-antiplasmin, which quickly inactivates free plasmin escaping from clots. Some α_2-antiplasmin is also cross-linked to fibrin by the action of factor XIIIa during clotting. This cross-linking may prevent excessive plasmin activity within clots. tPA and urokinase are rapidly cleared by the liver, which is another mechanism of preventing excessive fibrinolysis.

Excessive Bleeding

Unusual or excessive bleeding may be indicated by several different signs and symptoms. Patients may present with unexplained nosebleeds (epistaxis), excessive or prolonged menstrual blood flow (menorrhagia), or prolonged bleeding after minor cuts, tooth brushing or flossing, or trauma. Other patients may have unexplained skin lesions, including petechiae (small intradermal or mucosal hemorrhages), purpura (areas of mucosal or skin hemorrhage larger than petechiae), ecchymoses (bruises), or telangiectasias (dilated small vessels visible on skin or mucosa). Some critically ill patients may suddenly bleed from vascular punctures or skin lesions and have severe hemorrhage from these sites or from the GI or GU tract. In some patients, a laboratory test abnormality suggesting the susceptibility to excessive bleeding is found incidentally.

Etiology

Excessive bleeding can result from several mechanisms (see Table 109-2), including the following:

- Platelet disorders

- Coagulation disorders

- Defects in blood vessels

Platelet disorders may involve an abnormal number of platelets (typically too few platelets, although an extremely elevated platelet count may be associated either with thrombosis or with excessive bleeding), defective platelet function, or both. Coagulation disorders may be acquired or hereditary.

Overall, the most common causes of excessive bleeding include

- Severe thrombocytopenia

- Excessive anticoagulation with warfarin or heparin

- Liver disease (inadequate production of coagulation factors)

Evaluation

History: History of present illness should determine the bleeding sites, the amount and duration of bleeding, and the relationship of bleeding to any possible precipitating factors.

Review of systems should specifically query about bleeding from sites other than those volunteered (eg, patients complaining of easy bruising should be questioned about frequent nosebleeds, gum bleeding while tooth brushing, melena, hemoptysis, blood in stool or urine). Patients should be asked about symptoms of possible causes, including abdominal pain and diarrhea (GI illness); joint pain (connective tissue disorders); and amenorrhea and morning sickness (pregnancy).

Past medical history should seek known systemic conditions associated with defects in platelets or coagulation, particularly

• Severe infection, cancer, cirrhosis, HIV infection, pregnancy, SLE, or uremia

• Prior excessive or unusual bleeding or transfusions

• Family history of excessive bleeding

Drug history should be reviewed, particularly use of heparin, warfarin, aspirin, and NSAIDs.

Physical examination: Vital signs and general appearance can indicate hypovolemia

[Table 109-2. Some Causes of Excessive Bleeding]

(tachycardia, hypotension, pallor, diaphoresis) or infection (fever, tachycardia, hypotension with sepsis).

The skin and mucous membranes (nose, mouth, vagina) are examined for petechiae, purpura, and telangiectasias. GI bleeding can often be identified by digital rectal examination. Signs of bleeding in deeper tissues may include tenderness during movement and local swelling, muscle hematomas, and, for intracranial bleeding, confusion, stiff neck, focal neurologic abnormalities, or a combination of these findings.

Characteristic findings of alcohol abuse or liver disease are ascites, splenomegaly (secondary to portal hypertension), and jaundice.

Red flags: The following findings are of particular concern:

• Signs of hypovolemia or hemorrhagic shock

• Pregnancy or recent delivery

• Signs of infection or sepsis

Interpretation of findings: Bleeding in a patient taking warfarin, especially if there has been a recent increase in dose, is likely due to the drug. Telangiectasias on the face, lips, oral or nasal mucosa, and tips of the fingers and toes in a patient with a positive family history of excessive bleeding is likely hereditary hemorrhagic telangiectasia.

Bleeding from superficial sites, including skin and mucous membranes, suggests a quantitative or qualitative defect in platelets or a defect in blood vessels (eg, amyloidosis).

Bleeding into deep tissues (eg, hemarthroses, muscle hematomas, retroperitoneal hemorrhage) suggests a defect in coagulation (coagulopathy).

A family history of excessive bleeding suggests an inherited coagulopathy (eg, hemophilia), a qualitative

platelet disorder, a type of von Willebrand's disease (VWD), or hereditary hemorrhagic telangiectasia. Absence of a known family history does not, however, exclude an inherited disorder of hemostasis.

Bleeding in a patient who is pregnant or has recently delivered, who is in shock, or who has a serious infection suggests disseminated intravascular coagulation (DIC).

Bloody diarrhea and thrombocytopenia in a child with fever and GI symptoms suggest the hemolytic-uremic syndrome (HUS), which is often associated with infection by *Escherichia coli* O157:H7.

In a child, a palpable, purpuric rash on the extensor surfaces of the extremities suggests Henoch-Schonlein purpura, particularly if accompanied by fever, polyarthralgia, or GI symptoms.

Patients with known alcohol abuse or liver disease may have coagulopathy, splenomegaly, or thrombocytopenia.

In patients with a history of IV drug abuse, HIV infection should be considered.

Testing: Most patients require laboratory evaluation (see Table 109-3). The initial tests are

• CBC with platelet count

• Peripheral blood smear

• PT and PTT

Screening tests evaluate the components of hemostasis, including the number of circulating platelets and the plasma coagulation pathways. The most common screening tests for bleeding disorders are the platelet count, PT, and PTT. If results are abnormal, a specific test can usually pinpoint the defect. Determination of the level of fibrin degradation products measures in vivo activation of fibrinolysis.

[**Table 109-3.** Laboratory Tests of Hemostasis by Phase]

Prothrombin time (PT) screens for abnormalities in the extrinsic and common pathways of coagulation (plasma factors VII, X, V, prothrombin, and fibrinogen). The PT is reported as the international normalized ratio (INR), which reflects the ratio of the patient's PT to the laboratory's control value; the INR controls for differences in reagents among different laboratories. Because commercial reagents and instrumentation vary widely, each laboratory determines its own normal range for PT and PTT; a typical normal range for the PT is between 10 and 13 sec. An INR > 1.5 or a PT ≥ 3 sec longer than a laboratory's normal control value is usually abnormal and requires further evaluation. The INR is valuable in screening for abnormal coagulation in various acquired conditions (eg, vitamin K deficiency, liver disease, DIC). It is also used to monitor therapy with the oral vitamin K antagonist, warfarin.

Partial thromboplastin time (PTT) screens plasma for abnormalities in factors of the intrinsic and common pathways (prekallikrein; high mol wt kininogen; factors XII, XI, IX, VIII, X, and V; prothrombin; fibrinogen). The PTT tests for deficiencies of all clotting factors except factor VII (measured by the PT) and factor XIII. A typical normal range is 28 to 34 sec. A normal result indicates that at least 30% of all coagulation factors in the pathway are present in the plasma. Heparin prolongs the PTT, and the PTT is often used to monitor heparin therapy. Inhibitors that prolong the PTT include an autoantibody against factor VIII (see pp. 977 and 979) and antibodies against protein-phospholipid complexes (lupus anticoagulant—see pp. 973 and 979).

Prolongation of PT or PTT may reflect

• Factor deficiency

• Presence of an inhibitor of a component of the coagulation pathway

The PT and PTT do not become prolonged until one or more of the clotting factors tested are about 70% deficient. For determining if prolongation reflects a deficiency of one or more clotting factor or the presence of an inhibitor, the test is repeated after mixing the patient's plasma with normal plasma in a 1:1 ratio. Because this mixture provides about 50% of normal levels of all coagulation factors, failure of the mixture to correct almost completely the prolongation suggests the presence of an inhibitor in patient plasma.

The previously used bleeding time test is of doubtful reliability.

Normal results on initial tests exclude many bleeding disorders. The main exceptions are VWD and hereditary hemorrhagic telangiectasia. VWD is a common entity in which the associated deficiency of factor VIII is frequently insufficient to prolong the PTT. Patients who have normal initial test results, along with symptoms or signs of bleeding and a positive family history, should be tested for VWD by measuring plasma von Willebrand's factor (VWF) antigen, ristocetin cofactor activity (an indirect test for large VWF multimers), and factor VIII levels.

If **thrombocytopenia** is present, the peripheral blood smear often suggests the cause (see Table 108-2). If the smear is normal, patients should be tested for HIV. If the result of the HIV test is negative and the patient is not pregnant and has not taken a drug known to cause platelet destruction, then idiopathic thrombocytopenic purpura is likely. If there are signs of hemolysis (fragmented RBCs on smear, decreasing Hb level), thrombotic thrombocytopenic purpura (TTP) or HUS is suspected, although sometimes other hemolytic disorders can cause these findings. HUS occurs in children with hemorrhagic colitis. The Coombs' test is negative in TTP and HUS. If the CBC and peripheral blood smear demonstrate other cytopenias or abnormal WBCs, a hematologic abnormality affecting multiple cell types is suspected, and a bone marrow aspiration or biopsy is necessary for diagnosis.

Prolonged PTT with normal platelets and PT suggests hemophilia A or B. Factor VIII and IX assays are indicated. Inhibitors that prolong the PTT include an autoantibody against factor VIII and antibodies against protein-phospholipid complexes (lupus anticoagulant). Such inhibitors are suspected when a prolonged PTT does not correct upon 1:1 mixing with normal plasma.

Prolonged PT with normal platelets and PTT suggests factor VII deficiency. Congenital factor VII deficiency is rare; however, the short half-life of factor VII in plasma causes factor VII to decrease to low levels more rapidly than other vitamin K-dependent coagulation factors (eg, in patients given warfarin anticoagulation or in patients with incipient liver disease).

Prolonged PT and PTT with thrombocytopenia suggest DIC, especially in association with obstetric complications, sepsis, cancer, or shock. Confirmation is by finding elevated levels of D-dimers (or fibrin degradation products) and decreasing plasma fibrinogen levels on serial testing. Prolonged PT or PTT with normal platelet count occurs with liver disease or vitamin K deficiency or during anticoagulation with warfarin or unfractionated heparin. Liver disease is suspected based on history and is confirmed by finding elevation of serum aminotransferases and bilirubin; hepatitis testing is recommended.

Imaging tests are often required to detect occult bleeding in patients with bleeding disorders. For example, head CT should be done in patients with severe headaches, head injuries, or impairment of consciousness; and abdominal CT in patients with abdominal pain or other findings compatible with intraperitoneal or retroperitoneal hemorrhage.

Treatment

Treatment is directed at the underlying disorder and at any hypovolemia. For immediate treatment of bleeding due to a coagulopathy that has not yet been diagnosed, fresh frozen plasma, which contains all coagulation factors, should be infused pending definitive evaluation.

Key Points

• DIC should be suspected in patients with sepsis, shock, or complications of pregnancy or delivery.

- Drug causes are common, particularly mild platelet dysfunction caused by aspirin or NSAIDs.
- Easy bruising with no other clinical manifestations and normal laboratory test results is probably benign.

Chapter 110. Thrombotic Disorders

Introduction

In healthy people, homeostatic balance exists between procoagulant (clotting) forces and anticoagulant and fibrinolytic forces (see Ch. 109). Numerous genetic, acquired, and environmental factors can tip the balance in favor of coagulation, leading to the pathologic formation of thrombi in veins (eg, deep venous thrombosis [DVT]), arteries (eg, MI, ischemic stroke), or cardiac chambers. Thrombi can obstruct blood flow at the site of formation or detach and embolize to block a distant blood vessel (eg, pulmonary embolism, embolic stroke).

Etiology

Genetic defects that increase the propensity for venous thromboembolism include

• Factor V Leiden mutation, which causes resistance to activated protein C (APC)

• Prothrombin 20210 gene mutation

• Deficiency of protein C, protein S, protein Z, or antithrombin

Acquired defects also predispose to venous and arterial thrombosis (see Table 110-1).

Other disorders and environmental factors can increase the risk of thrombosis, especially if a genetic abnormality is also present.

Diagnosis

Diagnoses are summarized elsewhere in THE MANUAL specific to the location of the thrombus.

Predisposing factors: Predisposing factors should always be considered. In some cases, the condition is clinically obvious (eg, recent surgery or trauma, prolonged immobilization, cancer, generalized atherosclerosis). If no predisposing factor is readily apparent, further evaluation should be conducted in patients with

• Family history of venous thrombosis

• More than one episode of venous thrombosis

• Venous or arterial thrombosis before age 50

• Unusual sites of venous thrombosis (eg, cavernous sinus, mesenteric veins)

As many as half of all patients with spontaneous DVT have a genetic predisposition.

[**Table 110-1.** Acquired Causes of Thromboembolism]

Testing for predisposing congenital factors includes measurements of the quantity of activity of natural anticoagulant molecules in plasma and tests for specific gene defects. Testing begins with a group of screening tests, followed (if necessary) by specific assays.

Treatment

Treatment is summarized elsewhere in THE MANUAL specific to the location of the thrombus.

Factor V Resistance to Activated Protein C

APC (in complex with protein S) degrades factors Va and VIIIa, thus inhibiting coagulation. Any of several mutations to factor V make it resistant to inactivation by APC, increasing the tendency for thrombosis. Factor V Leiden is the most common of these mutations. Homozygous mutations increase the risk of thrombosis more than do heterozygous mutations.

Factor V Leiden as a single gene defect in European populations is present in about 5%, but it rarely occurs in native Asian or African populations. It is present in 20 to 60% of patients with spontaneous venous thrombosis.

Diagnosis is based on a functional plasma coagulation assay (the failure of patient plasma PTT to become prolonged in the presence of snake venom-activated patient protein C) and on molecular analysis of the factor V gene.

Treatment, if necessary, involves anticoagulation with heparin followed by warfarin.

Protein C Deficiency

Protein C is a vitamin K-dependent protein, as are coagulation factors VII, IX, and X, prothrombin, and proteins S and Z. Because APC degrades factors Va and VIIIa, APC is a natural plasma anticoagulant. Decreased protein C from genetic or acquired causes promotes venous thrombosis. Heterozygous deficiency of plasma protein C has a prevalence of 0.2 to 0.5%; about 75% of people with this defect experience a venous thromboembolism (50% by age 50). Homozygous or doubly heterozygous deficiency causes neonatal purpura fulminans, ie, severe neonatal disseminated intravascular coagulation (DIC). Acquired decreases occur in patients with liver disease or DIC, during cancer chemotherapy (including L-asparaginase administration), and during warfarin therapy.

Diagnosis is based on antigenic and functional plasma assays.

Patients with symptomatic thrombosis require anticoagulation with heparin or low mol wt heparin, followed by warfarin; use of the vitamin K antagonist, warfarin, as initial therapy occasionally causes thrombotic skin infarction by lowering vitamin K-dependent protein C levels before a therapeutic decrease has occurred in most vitamin K-dependent clotting factors. Neonatal purpura fulminans is fatal without replacement of protein C (using normal plasma or purified concentrate) and anticoagulation with heparin.

Protein S Deficiency

Protein S, a vitamin K-dependent protein, is a cofactor for APC-mediated cleavage of factors Va and VIIIa. Heterozygous deficiency of plasma protein S predisposes to venous thrombosis and is similar to protein C deficiency in genetic transmission, prevalence, laboratory testing, treatment, and precautions. Homozygous deficiency of protein S can cause neonatal purpura fulminans that is clinically indistinguishable from that caused by homozygous deficiency of protein C. Acquired deficiencies of protein S (and protein C) occur during DIC and warfarin therapy and after L-asparaginase administration.

Diagnosis is based on antigenic assays of total or free plasma protein S. (Free protein S is the form unbound to C4 binding protein.)

Protein Z Deficiency

Protein Z, another vitamin K-dependent protein, functions as a cofactor to down-regulate coagulation by forming a complex with the plasma protein, Z-dependent protease inhibitor (ZPI). The complex inactivates factors Xa, XI, and IX on phospholipids surfaces. The consequence of either protein Z or ZPI deficiency in the pathophysiology of thrombosis and fetal loss is unresolved; however, either defect may make thrombosis more likely if an affected patient also has another congenital coagulation abnormality (eg, factor V Leiden). Quantification of protein Z and ZPI is done in research laboratories by plasma electrophoresis and immunoblotting. It is not yet known whether anticoagulant therapy or prophylaxis is indicated in protein Z or ZPI deficiency.

Antithrombin Deficiency

Antithrombin is a protein that inhibits thrombin and factors Xa, IXa, and XIa. Heterozygous deficiency of plasma antithrombin has a prevalence of about 0.2 to 0.4%; about half of those affected develop venous thromboses. Homozygous deficiencies are probably lethal to the fetus in utero. Acquired deficiencies occur in patients with DIC, liver disease, or nephrotic syndrome and during heparin or L-asparaginase therapy.

Laboratory testing involves quantification of plasma inhibition of thrombin in the presence of heparin.

Oral warfarin is used for prophylaxis against venous thromboembolism.

Prothrombin 20210 Gene Mutation

A mutation of the prothrombin 20210 gene results in increased plasma prothrombin levels and increases the risk of venous thromboembolism. Treatment, if necessary, involves anticoagulation with heparin followed by warfarin.

Antiphospholipid Antibody Syndrome

(Anti-Cardiolipin Antibodies; Lupus Anticoagulant)

The antiphospholipid antibody syndrome consists of thrombosis and (in pregnancy) fetal demise associated with various autoimmune antibodies directed against one or more phospholipid-binding proteins (eg, β_2-glycoprotein I, prothrombin, annexin). These proteins normally bind to phospholipid membrane constituents and protect them from excessive coagulation activation. The autoantibodies displace the protective proteins and, thus, produce procoagulant endothelial cell surfaces and cause arterial or venous thromboses. In vitro clotting tests may paradoxically be prolonged because the antiprotein/phospholipid antibodies interfere with coagulation factor assembly and activation on the phospholipid components added to plasma to initiate the tests. The lupus anticoagulant is an antiphospholipid autoantibody that binds to protein-phospholipid complexes. It was initially recognized in patients with SLE, but these patients now account for a minority of patients with the autoantibody.

The lupus anticoagulant is suspected if the PTT is prolonged and does not correct immediately upon 1:1 mixing with normal plasma but does return to normal upon the addition of an excessive quantity of phospholipids (done by the hematology laboratory). Antiphospholipid antibodies in patient plasma are measured by immunoassays of IgG and IgM antibodies that bind to phospholipid-β_2-glycoprotein I complexes on microtiter plates.

Heparin, warfarin, and aspirin have been used for prophylaxis and treatment.

Hyperhomocysteinemia

Hyperhomocysteinemia may predispose to arterial thrombosis and venous thromboembolism, possibly because of injury to vascular endothelial cells. Plasma homocysteine levels are elevated ≥ 10-fold in homozygous cystathionine β-synthase deficiency. Milder elevations occur in heterozygous deficiency and in other abnormalities of folate metabolism, including methyltetrahydrofolate dehydrogenase deficiency. However, by far the most common causes of hyperhomocysteinemia are acquired deficiencies of folate, vitamin B_{12}, or vitamin B_6.

The diagnosis is established by measuring plasma homocysteine levels.

Plasma homocysteine levels may be normalized by dietary supplementation with folic acid, vitamin B_{12}, or vitamin B_6 (pyridoxine) alone or in combination; however, it is not clear that this therapy reduces the risk of arterial or venous thrombosis.

Chapter 111. Coagulation Disorders

Introduction

Abnormal bleeding can result from disorders of the coagulation system (see p. 963), of platelets, or of blood vessels. Disorders of coagulation can be acquired or hereditary. The major causes of acquired coagulation disorders are vitamin K deficiency (see p. 46), liver disease, disseminated intravascular coagulation, and development of circulating anticoagulants. Severe liver disease (eg, cirrhosis, fulminant hepatitis, acute fatty liver of pregnancy) may disturb hemostasis by impairing clotting factor synthesis. Because all coagulation factors are made in the liver, both the PT and PTT are elevated in severe liver disorders. (PT results are typically reported as INR.) Occasionally, decompensated liver disease also causes excessive fibrinolysis and bleeding due to decreased hepatic synthesis of α_2-antiplasmin.

The most common hereditary disorder of hemostasis is von Willebrand's disease (see p. 962). The most common hereditary coagulation disorders are the hemophilias.

Disseminated Intravascular Coagulation

(Consumption Coagulopathy; Defibrination Syndrome)

Disseminated intravascular coagulation (DIC) involves abnormal, excessive generation of thrombin and fibrin in the circulating blood. During the process, increased platelet aggregation and coagulation factor consumption occur. DIC that evolves slowly (over weeks or months) causes primarily venous thrombotic and embolic manifestations; DIC that evolves rapidly (over hours or days) causes primarily bleeding. Severe, rapidly evolving DIC is diagnosed by demonstrating thrombocytopenia, an elevated PTT and PT, increased levels of plasma D-dimer (or serum fibrin degradation products), and a decreasing plasma fibrinogen level. Treatment includes correction of the cause and replacement of platelets, coagulation factors (in fresh frozen plasma), and fibrinogen (in cryoprecipitate) to control severe bleeding. Heparin is used as therapy (or prophylaxis) in patients with slowly evolving DIC who have (or are at risk of) venous thromboembolism.

Etiology

DIC usually results from exposure of tissue factor to blood, initiating the coagulation cascade (see Fig. 109-2). DIC occurs in the following clinical circumstances:

- Complications of obstetrics (eg, abruptio placentae, saline-induced therapeutic abortion, retained dead fetus or products of conception, amniotic fluid embolism): Placental tissue with tissue factor activity enters or is exposed to the maternal circulation.

- Infection, particularly with gram-negative organisms: Gram-negative endotoxin causes generation or exposure of tissue factor activity in phagocytic, endothelial, and tissue cells.

- Cancer, particularly mucin-secreting adenocarcinomas of the pancreas and prostate and acute promyelocytic leukemia: Tumor cells express or release tissue factor.

- Shock due to any condition that causes ischemic tissue injury and release of tissue factor

Less common causes of DIC include severe tissue damage from head trauma, burns, frostbite, or gunshot wounds; complications of prostate surgery that allow prostatic material with tissue factor activity (along with plasminogen activators) to enter the circulation; venomous snake bites in which enzymes enter the circulation, activate one or several coagulation factors, and either generate thrombin or directly convert fibrinogen to fibrin; profound intravascular hemolysis; and aortic aneurysms or cavernous hemangiomas (Kasabach-Merritt syndrome) associated with vessel wall damage and areas of blood stasis.

Pathophysiology

Slowly evolving DIC primarily causes venous thromboembolic manifestations (eg, deep venous thrombosis, pulmonary embolism), although occasionally cardiac valve vegetations occur; abnormal bleeding is uncommon.

Severe, rapidly evolving DIC, in contrast, causes thrombocytopenia and depletion of plasma clotting factors and fibrinogen, which cause bleeding. Bleeding into organs, along with microvascular thromboses, may cause dysfunction and failure in multiple organs. Delayed dissolution of fibrin polymers by fibrinolysis may result in the mechanical disruption of RBCs, producing schistocytes and mild intravascular hemolysis (see p. 961).

Symptoms and Signs

In slowly evolving DIC, symptoms of venous thrombosis (see p. 2224) and pulmonary embolism (see p. 1908) may be present.

In severe, rapidly evolving DIC, skin puncture sites (eg, IV or arterial punctures) bleed persistently, ecchymoses form at sites of parenteral injections, and serious GI bleeding may occur.

Diagnosis

• Platelet count, PT, PTT, plasma fibrinogen, plasma D-dimer

DIC is suspected in patients with unexplained bleeding or venous thromboembolism, especially if a predisposing condition exists. If DIC is suspected, platelet count, PT, PTT, plasma fibrinogen level, and plasma D-dimer level (an indication of in vivo fibrin deposition and degradation) are obtained.

Slowly evolving DIC produces mild thrombocytopenia, a normal to minimally prolonged PT (results are typically reported as INR) and PTT, a normal or moderately reduced fibrinogen level, and an increased plasma D-dimer level. Because various disorders stimulate increased synthesis of fibrinogen as an acute-phase reactant, a declining fibrinogen level on 2 consecutive measurements can help make the diagnosis of DIC. Initial PTT values in slowly evolving DIC may actually be shorter than normal, probably because of the presence of activated coagulation factors in the plasma.

Severe, rapidly evolving DIC results in more severe thrombocytopenia, more prolonged PT and PTT, a rapidly declining plasma fibrinogen level, and a high plasma D-dimer level.

A factor VIII level can sometimes be helpful if severe, acute DIC must be differentiated from massive hepatic necrosis, which can cause similar abnormalities in coagulation studies. The factor VIII level is elevated in hepatic necrosis, because factor VIII is made in hepatocytes and released as they are destroyed; factor VIII is reduced in DIC because of the thrombin-induced generation of activated protein C, which proteolyses factor VIII.

Treatment

• Treatment of cause

• Possibly replacement therapy (eg, platelets, cryoprecipitate, fresh frozen plasma, natural anticoagulants)

• Sometimes heparin

Immediate correction of the cause is the priority (eg, broad-spectrum antibiotic treatment of suspected gram-negative sepsis, evacuation of the uterus in abruptio placentae). If treatment is effective, DIC should subside quickly. If bleeding is severe, adjunctive replacement therapy is indicated, consisting of platelet concentrates to correct thrombocytopenia; cryoprecipitate to replace fibrinogen and factor VIII; and fresh frozen plasma to increase levels of other clotting factors and natural anticoagulants (antithrombin, proteins C, S, and Z). The effectiveness of infusion of concentrates of antithrombin or activated protein C in severe, rapidly evolving DIC is unresolved.

Heparin is useful in the treatment of slowly evolving DIC with venous thrombosis or pulmonary embolism. Heparin usually is not indicated in rapidly evolving DIC with bleeding or bleeding risk, except in women with a retained dead fetus and evolving DIC with a progressive decrease in platelets, fibrinogen, and coagulation factors. In these patients, heparin is administered for several days to control DIC, increase fibrinogen and platelet levels, and decrease excessive coagulation factor consumption. Heparin is then stopped and the uterus evacuated.

Hemophilia

Hemophilias are common hereditary bleeding disorders caused by deficiencies of either clotting factor VIII or IX. The extent of factor deficiency determines the probability and severity of bleeding. Bleeding into deep tissues or joints usually develops within hours of trauma. The diagnosis is suspected in a patient with an elevated PTT and normal PT and platelet count; it is confirmed by specific factor assays. Treatment includes replacement of the deficient factor if acute bleeding is suspected, confirmed, or likely to develop (eg, before surgery).

Hemophilia A (factor VIII deficiency), which affects about 80% of patients with hemophilia, and hemophilia B (factor IX deficiency) have identical clinical manifestations, screening test abnormalities, and X-linked genetic transmission. Specific factor assays are required to distinguish the two.

Etiology

Hemophilia is an inherited disorder that results from mutations, deletions, or inversions affecting a factor VIII or factor IX gene. Because these genes are located on the X chromosome, hemophilia affects males almost exclusively. Daughters of men with hemophilia are obligate carriers, but sons are normal. Each son of a carrier has a 50% chance of having hemophilia, and each daughter has a 50% chance of being a carrier.

Pathophysiology

Normal hemostasis requires > 30% of normal factor VIII and IX levels. Most patients with hemophilia have levels < 5%. Carriers usually have levels of about 50%; rarely, random inactivation of their normal X chromosome in early embryonic life results in a carrier having factor VIII or IX levels of < 30%.

Most patients with hemophilia who were treated with plasma concentrates in the early 1980s were infected with HIV due to contaminated factor concentrates. Occasional patients developed immune thrombocytopenia secondary to HIV infection, which exacerbated bleeding.

Symptoms and Signs

Patients with hemophilia bleed into tissues (eg, hemarthroses, muscle hematomas, retroperitoneal hemorrhage). The bleeding may be immediate or occur slowly, depending on the extent of trauma and plasma level of factor VIII or IX. Pain often occurs as bleeding commences, sometimes before other signs of bleeding develop. Chronic or recurrent hemarthroses can lead to synovitis and arthropathy. Even a trivial blow to the head can cause intracranial bleeding. Bleeding into the base of the tongue can cause life-threatening airway compression.

Severe hemophilia (factor VIII or IX level < 1% of normal) causes severe bleeding throughout life, usually beginning soon after birth (eg, scalp hematoma after delivery or excessive bleeding after circumcision). Moderate hemophilia (factor levels 1 to 5% of normal) usually causes bleeding after minimal trauma. In mild hemophilia (factor levels 5 to 25% of normal), excessive bleeding may occur after surgery or dental extraction.

Diagnosis

• Platelet count, PT, PTT, factor VIII and IX assays

• Sometimes von Willebrand's factor activity and antigen and multimer composition

Hemophilia is suspected in patients with recurrent bleeding, unexplained hemarthroses, or a prolongation of the PTT. If hemophilia is suspected, PTT, PT, platelet count, and factor VIII and IX assays are obtained. In hemophilia, the PTT is prolonged, but the PT and platelet count are normal. Factor VIII and IX assays determine the type and severity of the hemophilia. Because factor VIII levels may also be reduced in von Willebrand's disease (VWD), von Willebrand's factor (VWF) activity, antigen, and multimer composition are measured in patients with newly diagnosed hemophilia A, particularly if the disorder is mild and a family history indicates that both male and female family members are affected. Determining if a female is a true carrier of hemophilia A is sometimes possible by measuring the factor VIII level. Similarly, measuring the factor IX level often identifies a carrier of hemophilia B. PCR analysis of DNA that comprises the factor VIII gene, available at specialized centers, can be used for diagnosis of the hemophilia A carrier state and for prenatal diagnosis of hemophilia A by chorionic villus sampling at 12 wk or amniocentesis at 16 wk. These procedures carry a 0.5 to 1% risk of miscarriage.

After repeated exposure to factor VIII replacement, about 15 to 35% of patients with hemophilia A develop factor VIII isoantibodies (alloantibodies) that inhibit the coagulant activity of any additional factor VIII infused. Patients should be screened for isoantibodies (eg, by measuring the degree of PTT shortening immediately after mixing the patient's plasma with an equal volume of normal plasma, and then by repeating the measurement after incubation for 1 h), especially before an elective procedure that requires replacement therapy. If isoantibodies are present, their titers can be measured by determining the extent of factor VIII inhibition by serial dilutions of patient plasma.

Treatment

• Replacement of deficient factor

• Sometimes antifibrinolytics

If symptoms suggest bleeding, treatment should begin immediately, even before diagnostic tests are completed. For example, treatment for headache that might indicate intracranial hemorrhage should begin before a CT scan is completed.

Replacement of the deficient factor is the primary treatment. In hemophilia A, the factor VIII level should be raised transiently to

• About 30% of normal to prevent bleeding after dental extraction or to abort an incipient joint hemorrhage

• 50% of normal if severe joint or IM bleeding is already evident

• 100% of normal before major surgery or if bleeding is intracranial, intracardiac, or otherwise life threatening

Repeated infusions at 50% of the initial calculated dose should then be given every 8 to 12 h to keep trough levels above 50% for 7 to 10 days after major surgery or life-threatening hemorrhage. Each unit/kg of factor VIII increases the factor VIII level by about 2%. Thus, to increase the level from 0% to 50%, about 25 units/kg are required.

Factor VIII can be given as purified factor VIII concentrate, which is derived from multiple donors. It undergoes viral inactivation, but inactivation may not eliminate parvovirus or hepatitis A. Recombinant factor VIII is free of viruses and is usually preferred unless patients are already seropositive for HIV or for hepatitis B or C virus.

In hemophilia B, factor IX can be given as a purified or recombinant viral-inactivated product every 24 h. The target levels of factor correction are the same as in hemophilia A. However, to achieve these levels, the dose must be higher than in hemophilia A because factor IX is smaller than factor VIII and, in contrast to VIII, has an extensive extravascular distribution.

Fresh frozen plasma contains factors VIII and IX. However, unless plasma exchange is done, sufficient whole plasma usually cannot be given to patients with severe hemophilia to raise factor VIII or IX to levels that prevent or control bleeding. Fresh frozen plasma should, therefore, be used only if rapid replacement therapy is necessary and factor concentrate is unavailable or the patient has a coagulopathy that is not yet defined precisely.

In patients with hemophilia who develop a factor VIII inhibitor, treatment is best accomplished using recombinant factor VIIa in repeated high doses (eg, 90 g/kg).

Adjunctive therapies may include desmopressin or an antifibrinolytic drug. As described for VWD (see p. 963), desmopressin may temporarily raise factor VIII levels. The patient's response should be tested before desmopressin is used therapeutically. Its use after minor trauma or before elective dental surgery may obviate replacement therapy. Desmopressin should be used only for patients with mild hemophilia A (basal factor VIII levels ≥ 5%) who have demonstrated responsiveness.

An antifibrinolytic agent (ε-aminocaproic acid 2.5 to 4 g po qid for 1 wk or tranexamic acid 1.0 to 1.5 g po tid or qid for 1 wk) should be given to prevent late bleeding after dental extraction or other oropharyngeal mucosal trauma (eg, tongue laceration).

Prevention

Patients should avoid aspirin and NSAIDs (both inhibit platelet function). Regular dental care is essential so that tooth extractions and other dental surgery can be avoided. Drugs should be given orally or IV; IM injections can cause hematomas. Patients with hemophilia should be vaccinated against hepatitis B.

Coagulation Disorders Caused by Circulating Anticoagulants

Circulating anticoagulants are usually autoantibodies that neutralize specific clotting factors in vivo (eg, an autoantibody against factor VIII or factor V) or inhibit protein-bound phospholipid in vitro. Occasionally, the latter type of autoantibody causes bleeding in vivo by binding prothrombin.

Circulating anticoagulants should be suspected in patients with excessive bleeding combined with either a prolonged PTT or PT that does not correct when the test is repeated with a 1:1 mixture of normal plasma and the patient's plasma.

Antiphospholipid antibodies (see p. 975) typically cause thrombosis. However, in a subset of patients, the antibodies bind to prothrombin-phospholipid complexes and induce hypoprothrombinemia and bleeding.

Factor VIII Anticoagulants

Isoantibodies to factor VIII develop in about 15 to 35% of patients with severe hemophilia A as a complication of repeated exposure to normal factor VIII molecules during replacement therapy (see p. 978). Factor VIII autoantibodies also arise occasionally in patients without hemophilia, eg, in postpartum women as a manifestation of an underlying systemic autoimmune disorder or of transiently disordered immune regulation, or in elderly patients without overt evidence of other underlying disorders. Patients with a factor VIII anticoagulant can develop life-threatening hemorrhage.

Plasma containing a factor VIII antibody has a prolonged PTT that does not correct when normal plasma or another source of factor VIII is added in a 1:1 mixture to the patient's plasma. Testing is done immediately after mixture and again after incubation.

Therapy with cyclophosphamide and corticosteroids may suppress autoantibody production in patients without hemophilia. In postpartum women, the autoantibodies may disappear spontaneously. Management of acute hemorrhage in patients with hemophilia who have factor VIII isoantibodies or autoantibodies is by recombinant factor VIIa (see above).

Uncommon Hereditary Coagulation Disorders

Most hereditary coagulation disorders other than hemophilia are rare autosomal recessive conditions that cause disease only in homozygous people (see Table 111-1). Factor XI deficiency is uncommon in the general population but common in descendants of European Jews (gene frequency about 5 to 9%). Bleeding typically occurs after significant injuries, including trauma or surgery, in people who are homozygotes or compound heterozygotes.

Severe deficiency of α_2-antiplasmin (1 to 3% of normal), the major physiologic inhibitor of plasmin, can also cause bleeding. Diagnosis

[**Table 111-1.** Screening Laboratory Test Results in Inherited Defects in Blood Coagulation]

is based on a specific α_2-antiplasmin assay. ε-Aminocaproic acid or tranexamic acid is used to control or prevent acute bleeding. Heterozygous people with α_2-antiplasmin levels of 40 to 60% of normal can occasionally experience excessive surgical bleeding if secondary fibrinolysis is extensive (eg, in patients who have had open prostatectomy).

Chapter 112. Bleeding Due to Abnormal Blood Vessels

Introduction

Bleeding may result from abnormalities in platelets, coagulation factors, or blood vessels. Vascular bleeding disorders result from defects in blood vessels, typically causing petechiae, purpura, and bruising but seldom leading to serious blood loss. Bleeding may result from deficiencies of vascular and perivascular collagen in Ehlers-Danlos syndrome and in other rare hereditary connective tissue disorders (eg, pseudoxanthoma elasticum, osteogenesis imperfecta, Marfan syndrome—see p. 2908). Hemorrhage may be a prominent feature of scurvy (see p. 40) or of Henoch-Schonlein purpura, a hypersensitivity vasculitis common during childhood (see p. 321). In vascular bleeding disorders, tests of hemostasis are usually normal. Diagnosis is clinical.

Autoerythrocyte Sensitization

(Gardner-Diamond Syndrome)

Autoerythrocyte sensitization is a rare disorder affecting women. It is characterized by local pain and burning preceding painful ecchymoses that occur primarily on the extremities.

Autoerythrocyte sensitization typically occurs in white women who are experiencing emotional stress or who have concomitant psychologic illness. Episodes of ecchymosis are painful and can occur spontaneously or after trauma or surgery. Bruising can occur on different sites of the body from where the trauma occurs. Tests of the coagulation system are normal.

In women with autoerythrocyte sensitization, intradermal injection of 0.1 mL of autologous RBCs or RBC stroma may result in pain, swelling, and induration at the injection site. This result suggests that escape of RBCs into the tissues is involved in the pathogenesis of the lesion. However, most patients also have associated severe psychoneurotic symptoms. In addition, psychogenic factors, such as self-induced purpura, seem related to the pathogenesis of the syndrome in some patients.

Diagnosis is based on examination of the site of intradermal injection of autologous RBCs and of a separate control injection site (without RBCs) 24 to 48 h after injection. Excoriation, which can complicate the test's interpretation, is prevented by making both sites difficult for the patient to reach. Treatment is psychiatric intervention and therapy.

Dysproteinemias Causing Vascular Purpura

Conditions that cause an abnormal protein content in the blood, typically in the form of immunoglobulins, can affect vascular fragility and lead to purpura.

Amyloidosis (see p. 905) causes amyloid deposition within vessels in the skin and subcutaneous tissues, which may increase vascular fragility, producing purpura. In some patients, coagulation factor X is adsorbed by amyloid and becomes deficient, but this deficiency is usually not the cause of bleeding. Periorbital purpura or a purpuric rash that develops in a nonthrombocytopenic patient after gentle stroking of the skin suggests amyloidosis.

Cryoglobulinemia produces immunoglobulins that precipitate when plasma is cooled (ie, cryoglobulins) while flowing through the skin and subcutaneous tissues of the extremities. Monoclonal immunoglobulins formed in Waldenstrom's macroglobulinemia or in multiple myeloma (see p. 1029) occasionally behave as cryoglobulins, as may mixed IgMl-gG immune complexes formed in some chronic infectious diseases, most commonly hepatitis C. Cryoglobulinemia can lead to small-vessel vasculitis, which can cause purpura. Cryoglobulins can be detected by laboratory testing.

Hypergammaglobulinemic purpura is a vasculitic purpura that primarily affects women. Recurrent crops of small, palpable purpuric lesions develop on the lower legs. These lesions leave small residual brown spots. Many patients have manifestations of an underlying immunologic disorder (eg, Sjogren's syndrome, SLE). The diagnostic finding is a polyclonal increase in IgG (broad-based or diffuse

hypergammaglobulinemia on serum protein electrophoresis).

Hyperviscosity syndrome (see p. 1027) resulting from a markedly elevated plasma IgM concentration may also result in purpura and other forms of abnormal bleeding (eg, profuse epistaxis) in patients with Waldenstrom's macroglobulinemia.

Hereditary Hemorrhagic Telangiectasia

(Rendu-Osler-Weber Syndrome)

Hereditary hemorrhagic telangiectasia is a hereditary disorder of vascular malformation transmitted as an autosomal dominant trait affecting men and women.

Symptoms and Signs

The most characteristic lesions are small red-to-violet telangiectatic lesions on the face, lips, oral and nasal mucosa, and tips of the fingers and toes (see Plate 56). Similar lesions may be present throughout the mucosa of the GI tract, resulting in recurrent GI bleeding. Patients may experience recurrent, profuse nosebleeds. Some patients have pulmonary arteriovenous fistulas. These fistulas may cause significant right-to-left shunts, which can result in dyspnea, fatigue, cyanosis, or polycythemia. However, the first sign of their presence may be a brain abscess, transient ischemic attack, or stroke as a result of infected or noninfected emboli. Cerebral or spinal arteriovenous malformations occur in some families and may cause subarachnoid hemorrhage, seizures, or paraplegia.

Diagnosis

• Clinical evaluation

• Sometimes endoscopy or angiography

Diagnosis is based on the finding of characteristic arteriovenous malformations on the face, mouth, nose, and digits. Endoscopy or angiography is sometimes needed, however. Laboratory findings are usually normal except for iron deficiency anemia in most patients.

Screening: If a family history of pulmonary or cerebral arteriovenous malformations exists, screening at puberty and at the end of adolescence with pulmonary CT or cerebral MRI is recommended.

Treatment

• Sometimes laser ablation, surgical resection, or embolotherapy

• Supplemental iron therapy

• Possibly blood transfusions

Treatment for most patients is supportive, but accessible telangiectases (eg, in the nose or GI tract via endoscopy) may be treated with laser ablation. Arteriovenous fistulas may be treated by surgical resection or embolotherapy. Repeated blood transfusions may be needed; therefore, immunization with hepatitis B vaccine is important. Most patients require continuous iron therapy to replace iron lost in repeated mucosal bleeding; some patients require parenteral iron (see Iron Deficiency Anemia on p. 924). Treatment with drugs that inhibit fibrinolysis, such as aminocaproic acid, may be beneficial.

Purpura Simplex

(Easy Bruising)

Purpura simplex is increased bruising that results from vascular fragility.

Purpura simplex is extremely common. The cause and mechanism are unknown; it may represent a heterogeneous group of disorders or merely a variation of normal.

The disorder usually affects women. Bruises develop on the thighs, buttocks, and upper arms in people without known trauma. The history usually reveals no other abnormal bleeding, but easy bruising may be present in family members. Serious bleeding does not occur. The platelet count and tests of platelet function, blood coagulation, and fibrinolysis are normal.

No drug prevents the bruising; patients are often advised to avoid aspirin and aspirin-containing drugs, but there is no evidence that bruising is related to or worsened by their use. Patients should be reassured that the condition is not serious.

Senile Purpura

Senile purpura causes ecchymoses and results from increased vessel fragility due to connective tissue damage to the dermis caused by chronic sun exposure and aging.

Senile purpura typically affects elderly patients as their dermal tissues atrophy and blood vessels become more fragile. Patients develop persistent dark purple ecchymoses, which are characteristically confined to the extensor surfaces of the hands and forearms. New lesions appear without known trauma and then resolve over several days, leaving a brownish discoloration caused by deposits of hemosiderin; this discoloration may clear over weeks to months or may be permanent. The skin and subcutaneous tissue of the involved area often appear thinned and atrophic. No treatment hastens lesion resolution or is needed. Although cosmetically displeasing, the disorder has no health consequences.

Chapter 113. Spleen Disorders

Introduction

By structure and function the spleen is like 2 organs. The white pulp, consisting of periarterial lymphatic sheaths and germinal centers, acts as an immune organ. The red pulp, consisting of macrophages and granulocytes lining vascular spaces (the cords and sinusoids), acts as a phagocytic organ.

The white pulp is a site of production and maturation of B and T cells. B cells in the spleen generate protective humoral antibodies; in certain autoimmune disorders (eg, immune thrombocytopenic purpura [ITP], Coombs'-positive immune hemolytic anemias), inappropriate autoantibodies to circulating blood elements also may be synthesized.

The red pulp removes antibody-coated bacteria, senescent or defective RBCs, and antibody-coated blood cells (as may occur in immune cytopenias such as ITP, Coombs'-positive hemolytic anemias, and some neutropenias). The red pulp also serves as a reservoir for blood elements, especially WBCs and platelets. During its culling and pitting of RBCs, the spleen removes inclusion bodies, such as Heinz bodies (precipitates of insoluble globin), Howell-Jolly bodies (nuclear fragments), and whole nuclei; thus, after splenectomy or in the functionally hyposplenic state, RBCs with these inclusions appear in the peripheral circulation. Hematopoiesis normally occurs in the red pulp only during fetal life. Beyond fetal life, hematopoiesis may occur if injury to bone marrow (eg, by fibrosis or tumors) allows hematopoietic stem cells to circulate and repopulate the adult spleen (see Primary Myelofibrosis on p. 999 and Myelodysplastic Syndrome on p. 1014).

Splenomegaly

Splenomegaly is almost always secondary to other disorders. Its causes are myriad, as are the many possible ways of classifying them (see
Table 113-1). In temperate climates, the most common causes are

• Myeloproliferative disorders

• Lymphoproliferative disorders

• Storage diseases (eg, Gaucher's disease)

• Connective tissue disorders

In the tropics, the most common causes are

• Infectious diseases (eg, malaria, kala-azar)

If splenomegaly is massive (spleen palpable 8 cm below the costal margin), the cause is usually chronic lymphocytic leukemia, non-Hodgkin lymphoma, chronic myelocytic leukemia, polycythemia vera, myelofibrosis with myeloid metaplasia, or hairy cell leukemia.

Splenomegaly can lead to cytopenia (see Hypersplenism on p. 985).

Evaluation

History: At presentation, most of the symptoms result from the underlying disorder. However, splenomegaly itself may cause early satiety by encroachment of the enlarged spleen on the stomach. Fullness and left upper quadrant abdominal pain are also possible. Severe pain suggests splenic infarction. Recurrent infections, symptoms of anemia, or bleeding manifestations suggest cytopenia and possible hypersplenism.

Physical examination: The sensitivity for detection of ultrasound-documented splenic enlargement is 60 to 70% for palpation and 60 to 80% for percussion. Up to 3% of normal,

[**Table 113-1.** Common Causes of Splenomegaly*]

thin, people have a palpable spleen. Also, a palpable left upper quadrant mass may indicate a problem other than an enlarged spleen.

Other helpful signs include a splenic friction rub that suggests splenic infarction and epigastric and splenic bruits that suggest congestive splenomegaly. Generalized adenopathy may suggest a myeloproliferative, lymphoproliferative, infectious, or autoimmune disorder.

Testing: If confirmation of splenomegaly is necessary because the examination is equivocal, ultrasonography is the test of choice because of its accuracy and low cost. CT and MRI may provide more detail of the organ's consistency. MRI is especially useful in detecting portal or splenic vein thromboses. Nuclear scanning is accurate and can identify accessory splenic tissue but is expensive and cumbersome to do.

Specific causes suggested clinically should be confirmed by appropriate testing (see elsewhere in THE MANUAL). If no cause is suggested, the highest priority is exclusion of occult infection, because early treatment affects the outcome of infection more than it does most other causes of splenomegaly. Testing should be thorough in areas of high geographic prevalence of infection or if the patient appears to be ill. CBC, blood cultures, and bone marrow examination and culture should be considered. If the patient is not ill, has no symptoms besides those due to splenomegaly, and has no risk factors for infection, the extent of testing is controversial but probably includes CBC, peripheral blood smear, liver function tests, and abdominal CT. Flow cytometry of peripheral blood is indicated if lymphoma is suspected.

Specific peripheral blood findings may suggest underlying disorders (eg, lymphocytosis in chronic lymphocytic leukemia; leukocytosis and immature forms in other leukemias). Excessive basophils, eosinophils, or nucleated or teardrop RBCs suggest myeloproliferative disorders. Cytopenias suggest hypersplenism. Spherocytosis suggests hypersplenism or hereditary spherocytosis. Liver function test results are diffusely abnormal in congestive splenomegaly with cirrhosis; an isolated elevation of serum alkaline phosphatase suggests hepatic infiltration, as in myeloproliferative and lymphoproliferative disorders and miliary TB.

Some other tests may be useful, even in asymptomatic patients. Serum protein electrophoresis identifying a monoclonal gammopathy or decreased immunoglobulins suggest lymphoproliferative disorders or amyloidosis; diffuse hypergammaglobulinemia suggests chronic infection (eg, malaria, kala-azar, brucellosis, TB) or cirrhosis with congestive splenomegaly, sarcoidosis, or connective tissue disorders. Elevation of serum uric acid suggests a myeloproliferative or lymphoproliferative disorder. Elevation of WBC alkaline phosphatase suggests a myeloproliferative disorder, whereas decreased levels suggest chronic myelocytic leukemia.

If testing reveals no abnormalities other than splenomegaly, the patient should be reevaluated at intervals of 6 to 12 mo or when new symptoms develop.

Treatment

Treatment is directed at the underlying disorder. The enlarged spleen itself needs no treatment unless severe hypersplenism is present. Patients with palpable or very large spleens probably should avoid contact sports to decrease the risk of splenic rupture.

Hypersplenism

Hypersplenism is cytopenia caused by splenomegaly.

Hypersplenism is a secondary process that can arise from splenomegaly of almost any cause (see Table 113-1). Splenomegaly increases the spleen's mechanical filtering and destruction of RBCs and often of WBCs and platelets. Compensatory bone marrow hyperplasia occurs in those cell lines that are reduced in the circulation.

Symptoms and Signs

Splenomegaly is the hallmark; spleen size correlates with the degree of anemia. The spleen can be expected to extend about 2 cm beneath the costal margin for each 1-g decrease in Hb. Other clinical findings usually result from the underlying disorder.

Diagnosis

Hypersplenism is suspected in patients with splenomegaly and anemia or cytopenias. Evaluation is similar to that of splenomegaly (see p. 984).

Unless other mechanisms coexist to compound their severity, anemia and other cytopenias are modest and asymptomatic (eg, platelet counts, 50,000 to 100,000/μL; WBC counts, 2500 to 4000/μL with normal WBC differential count). RBC morphology is generally normal except for occasional spherocytosis. Reticulocytosis is usual.

Treatment

• Possibly splenic ablation (splenectomy or radiation therapy)

• Vaccination for splenectomized patients

Treatment is directed at the underlying disorder. However, if hypersplenism is the only serious manifestation of the disorder (eg, Gaucher's disease), splenic ablation by splenectomy or radiation therapy may be indicated (see Table 113-2). Because the intact spleen protects against serious infections with encapsulated bacteria, splenectomy should be avoided whenever possible, and patients undergoing splenectomy require vaccination against infections caused by *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. After splenectomy, patients are particularly susceptible to severe sepsis. Patients who develop fever should receive empiric antibiotics.

Splenic Injury

Splenic injury usually results from blunt abdominal trauma.

Significant impact (eg, motor vehicle crash) can damage the spleen, as can penetrating trauma (eg, knife wound, gunshot wound). Splenic enlargement as a result of fulminant Epstein-Barr viral disease (infectious mononucleosis or posttransplant Epstein-Barr virus-mediated pseudolymphoma) predisposes to injury with minimal trauma or even spontaneously. Splenic injuries range from subcapsular hematomas and small capsular lacerations to deep parenchymal lacerations, crush injury, and avulsion from the pedicle.

[**Table 113-2.** Indications for Splenectomy or Radiation Therapy in Hypersplenism]

The main immediate consequence is hemorrhage into the peritoneal cavity. The amount of hemorrhage may be small or large, depending on the nature and degree of injury. Many small lacerations, particularly in children, cease bleeding spontaneously. Larger injuries hemorrhage extensively, often causing hemorrhagic shock. A splenic hematoma sometimes ruptures, usually in the first few days, although rupture can occur from hours to even months after injury.

Symptoms and Signs

The manifestations of major hemorrhage, including hemorrhagic shock, abdominal pain, and distention, are usually clinically obvious. Lesser hemorrhage causes left upper quadrant abdominal pain, which sometimes radiates to the shoulder. Patients with unexplained left upper quadrant pain, particularly if there is evidence of hypovolemia or shock, should be asked about recent trauma.

Diagnosis

The diagnosis is confirmed with CT in stable patients and with bedside (point of care) ultrasonography or exploratory laparotomy in unstable patients.

Treatment

Treatment has traditionally been splenectomy. However, splenectomy should be avoided if possible, particularly in children, to avoid the resulting permanent susceptibility to bacterial infections. Most small, and some moderatesized lacerations in stable patients (particularly children) are managed with hospital observation and sometimes transfusion rather than surgery. When surgery is needed, the spleen can be surgically repaired in a few cases, but splenectomy is still the main surgical treatment.

Chapter 114. Eosinophilic Disorders

Introduction

Eosinophils are granulocytes derived from the same progenitor cells as monocytesmacrophages, neutrophils, and basophils. The precise functions of eosinophils are unknown. Although they are phagocytic, eosinophils are less efficient than neutrophils in killing intracellular bacteria. And although eosinophilia commonly accompanies helminthic infections and eosinophils are toxic to helminths in vitro, there is no direct evidence that they kill parasites in vivo. Eosinophils may modulate immediate hypersensitivity reactions by degrading or inactivating mediators released by mast cells, such as histamine, leukotrienes (which may cause vasoconstriction and bronchoconstriction), lysophospholipids, and heparin. Prolonged eosinophilia may result in tissue damage by mechanisms that are not fully understood.

Eosinophil granules contain major basic protein and eosinophil cationic protein that are toxic to several parasites and to mammalian cells. These proteins bind heparin and neutralize its anticoagulant activity. Eosinophil-derived neurotoxin can severely damage myelinated neurons. Eosinophil peroxidase, which differs significantly from peroxidase of other granulocytes, generates oxidizing radicals in the presence of hydrogen peroxide and a halide. Charcot-Leyden crystals are primarily composed of phospholipase B and are located in sputum, tissues, and stool in disorders in which there is eosinophilia (eg, asthma, eosinophilic pneumonia).

The normal peripheral blood eosinophil count is < 350/µL, with diurnal levels that vary inversely with plasma cortisol levels; the peak occurs at night and the trough in the morning. The eosinophil count can decrease with stress, with use of β-blockers or corticosteroids, and sometimes with bacterial or viral infections. The count can increase with allergic disorders, with certain infections (typically parasitic), and from numerous other causes (see below). The circulating half-life of eosinophils is 6 to 12 h, with most eosinophils residing in tissues (eg, the upper respiratory and GI tracts, skin, uterus).

Eosinophil production appears to be regulated by T cells through the secretion of the hematopoietic growth factors granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-3 (IL-3), and interleukin-5 (IL-5). Although GM-CSF and IL-3 also increase the production of other myeloid cells, IL-5 increases eosinophil production exclusively.

Eosinophilia

Eosinophilia is defined as a peripheral blood eosinophil count > 450/µL. Causes and associated disorders are myriad but often represent an allergic reaction or parasitic infection. Diagnosis involves selective testing directed at clinically suspected causes. Treatment is directed at the cause.

Eosinophilia has features of an immune response: an agent such as *Trichinella spiralis* invokes a primary response with relatively low levels of eosinophils, whereas repeated exposures result in an augmented or secondary eosinophilic response. Several compounds released by mast cells and basophils induce IgE-mediated eosinophil production. Such substances include eosinophil chemotactic factor of anaphylaxis, leukotriene B4, complement complex (C5-C6-C7), and histamine (over a narrow range of concentration).

Eosinophilia itself does not cause symptoms. However, occasionally patients with very severe eosinophilia (eg, eosinophil counts of > 100,000/µL), usually with eosinophilic leukemia, develop complications of hyperleukocytosis (see p. 990).

Etiology

Eosinophilia may be primary (ie, clonal proliferation of eosinophils associated with hematologic disorders such as leukemias and myeloproliferative disorders), secondary to (or associated with) numerous nonhematologic disorders (see Table 114-1), or idiopathic (if other causes cannot be identified).

The **most common cause** in the US is

• Allergic or atopic disorders (typically respiratory or dermatologic)

Other common causes include

• Infections (typically parasitic)

• Certain tumors (hematologic or solid, benign or malignant)

Almost any parasitic invasion of tissues can elicit eosinophilia, but protozoa and noninvasive metazoa usually do not.

Of the tumors, Hodgkin lymphoma may elicit marked eosinophilia, whereas eosinophilia is less common in non-Hodgkin lymphoma, chronic myelocytic leukemia, and

[**Table 114-1.** Important Disorders and Treatments Associated with Eosinophilia]

acute lymphoblastic leukemia. Ovarian cancer is the most commonly associated solid tumor.

The pulmonary infiltrates with eosinophilia syndrome comprises a spectrum of clinical manifestations characterized by peripheral eosinophilia and eosinophilic pulmonary infiltrates (see p. 1953) but is usually of unknown cause.

Patients with eosinophilic drug reactions may be asymptomatic or have various syndromes, including interstitial nephritis, serum sickness, cholestatic jaundice, hypersensitivity vasculitis, and immunoblastic lymphadenopathy. Several hundred patients were reported to have developed an eosinophilia-myalgia syndrome after taking L-tryptophan for sedation or psychotropic support. This syndrome was probably caused by a contaminant rather than by L-tryptophan. The symptoms (severe muscle pain, tenosynovitis, muscle edema, rash) lasted weeks to months, and several deaths occurred.

Evaluation

The number of possible causes and associated disorders is very large. Common causes (eg, allergic, infectious, neoplastic disorders) should be considered first, but even they are often difficult to identify; a thorough history and physical examination are always required.

History: The questions most likely to be helpful pertain to the following:

• Travel (suggesting possible parasite exposure)

• Allergies

• Drug use

• Use of herbal products and dietary supplements, including L-tryptophan

• Systemic symptoms (eg, fever, weight loss, myalgias, arthralgias, rashes, lymphadenopathy)

Systemic symptoms suggest that a minor allergic or drug cause is less likely, and a detailed evaluation for an infectious, neoplastic, connective tissue, or other systemic disorder should be done. Other important parts of the history include family history of blood dyscrasias (eg, plasma cell disorders) and a complete review of systems, including symptoms of allergic, pulmonary, cardiac, GI, and neurologic dysfunction.

Physical examination: General physical examination is done, including the heart, skin, and neurologic and pulmonary systems. Certain physical findings may suggest causes or associated disorders. Examples include rash (allergic, dermatologic, or vasculitic disorders), abnormal lung findings (asthma, lung infections, or syndromes of pulmonary infiltration with eosinophilia), and generalized lymphadenopathy or

splenomegaly (myeloproliferative disorders or cancer).

Testing: Eosinophilia is typically recognized when CBC is done for other reasons. Additional testing often includes the following:

• Stool ova and parasite testing

• Other tests to detect organ damage or for specific causes based on clinical findings

When the CBC indicates eosinophilia, an absolute eosinophil count is rarely needed.

In general, if a drug or allergic cause is not clinically suspected, 3 stool specimens should be examined for ova and parasites; however, negative findings do not rule out a parasitic cause (eg, trichinosis requires a muscle biopsy; visceral larva migrans and filarial infections require other tissue biopsies; duodenal aspirates may be needed to exclude specific parasites, eg, *Strongyloides* sp—see p. 1350).

Other specific diagnostic tests are determined by the clinical findings (particularly travel history) and may include chest x-ray, urinalysis, liver and kidney function tests, and serologic tests for parasitic and connective tissue diseases. If patients have generalized lymphadenopathy, splenomegaly, or systemic symptoms, blood tests are done; an elevated serum vitamin B_{12} level, low WBC alkaline phosphatase level, or abnormalities on the peripheral blood smear suggest an underlying myeloproliferative disorder, in which case a bone marrow aspirate and biopsy with cytogenetic studies may be helpful. Also, if routine evaluation does not reveal a cause, tests are done to detect organ damage. Testing can include some of the tests previously mentioned as well as LDH and liver function tests (suggesting liver damage or possibly a myeloproliferative disorder), echocardiogram, and pulmonary function tests.

Treatment

• Sometimes corticosteroids

Corticosteroid treatment of hypereosinophilic syndrome is discussed on p. 992.

Drugs known to be associated with eosinophilia are stopped. Other identified causes are treated.

If no cause is detected, the patient is followed for complications. A brief trial with low-dose corticosteroids may lower the eosinophil count if eosinophilia is secondary (eg, to allergy, connective tissue disorders, or parasitic infection) rather than primary. Such a trial is indicated if eosinophilia is persistent and progressive in the absence of a treatable cause.

Hypereosinophilic Syndrome

(Idiopathic Hypereosinophilic Syndrome)

Hypereosinophilic syndrome (HES) is a condition characterized by peripheral blood eosinophilia with manifestations of organ system involvement or dysfunction directly related to eosinophilia in the absence of parasitic, allergic, or other causes of eosinophilia. Symptoms are myriad, depending on which organs are dysfunctional. Diagnosis involves excluding other causes of eosinophilia and bone marrow and genetic tests. Treatment usually begins with prednisone and, in one common subtype, includes imatinib.

HES is traditionally defined by peripheral blood eosinophilia > 1500/μL persisting ≥6 mo. HES was previously considered to be idiopathic but is now known to result from various disorders, some of which have known causes. One limitation of the traditional definition is that it does not include those patients with some of the same abnormalities (eg, genetic defects) that are known causes of HES and who do not fulfill the traditional HES diagnostic criteria for degree or duration of eosinophilia. Another limitation is that some patients with eosinophilia and organ damage that characterize HES require treatment earlier than the 6 mo necessary to confirm the traditional diagnostic criteria.

HES is rare, has an unknown prevalence, and most often affects people age 20 through 50. Only some patients with prolonged eosinophilia develop organ dysfunction that characterizes hypereosinophilic syndrome. Although any organ may be involved, the heart, lungs, spleen, skin, and nervous system are typically affected. Cardiac involvement often causes morbidity and mortality.

Subtypes: There are two broad subtypes (see Table 114-2):

• Myeloproliferative variant

• Lymphoproliferative variant

The **myeloproliferative variant** is often associated with a small interstitial deletion in chromosome 4 and the *FIPILI/PDGFRA*-associated fusion gene (reflecting tyrosine kinase activity that can transform hematopoietic cells). Patients often have

• Splenomegaly

• Thrombocytopenia

• Anemia

• Elevated serum vitamin B_{12} levels

• Hypogranular or vacuolated eosinophils

• Myelofibrosis

[**Table 114-2.** Subtypes of Hypereosinophilic Syndrome]

Patients with this subtype often develop endomyocardial fibrosis and may rarely develop acute myeloid or lymphoblastic leukemia. Patients with the *FIPILI/PDGFRA*-associated fusion gene are more often males and may be responsive to imatinib.

The **lymphoproliferative variant** is associated with a clonal population of T cells with aberrant phenotype. Patients more often have

• Angioedema, skin abnormalities, or both

• Hypergammaglobulinemia (especially IgE)

• Circulating immune complexes (sometimes with serum sickness)

They also more often respond favorably to corticosteroids and occasionally develop T-cell lymphoma.

Other HES variants include chronic eosinophilic leukemia, Gleich's syndrome (cyclical eosinophilia and angioedema), familial hypereosinophilic syndrome mapped to 5q 31-33, and other organ-specific syndromes. Hyperleukocytosis may occur in patients with eosinophilic leukemia and very high eosinophil counts (eg, > 100,000 cells/µL). Eosinophils can form aggregates that occlude small blood vessels, causing tissue ischemia and microinfarctions. Common manifestations include brain or lung hypoxia (eg, encephalopathy, dyspnea or respiratory failure).

Symptoms and Signs

Symptoms are diverse and depend on which organs are dysfunctional (see Table 114-3).

Occasionally, patients with very severe eosinophilia (eg, eosinophil counts of > 100,000/µL) develop

complications of hyperleukocytosis, such as manifestations of brain or lung hypoxia (eg, encephalopathy, dyspnea or respiratory failure).

Diagnosis

• Exclusion of secondary eosinophilia

• Tests to identify organ damage

• Bone marrow examination with cytogenetics

Evaluation for HES should be considered in patients who have peripheral blood eosinophilia > 1500/µL present on more than one occasion that is unexplained, particularly when there are manifestations of organ damage. Testing to exclude disorders causing eosinophilia should be done (see p. 990). Further evaluation should include blood chemistries (including liver enzymes, creatine kinase, renal function, and troponin), ECG; echocardiography; pulmonary function tests; and CT of the chest, abdomen, and pelvis. Bone marrow aspirate and biopsy with flow cytometry, cytogenetics, and reverse transcriptase-PCR or fluorescence in situ hybridization (FISH) is done to identify the *FIPILI/PDGFRA*-associated fusion gene and other possible causes of eosinophilia (eg, *BCR-ABL* abnormalities characteristic of chronic myelogenous leukemia).

Prognosis

Death usually results from organ, particularly heart, dysfunction. Cardiac involvement

[**Table 114-3.** Abnormalities in Patients with Hypereosinophilic Syndrome]

is not predicted by the degree or duration of eosinophilia. Prognosis varies depending on response to therapy. Response to imatinib improves the prognosis among patients with the *FIPILI/PDGFRA*-associated fusion gene. Current therapy has improved prognosis.

Treatment

• Corticosteroids for hypereosinophilia and often for ongoing treatment of organ damage

• Imatinib for patients with the *FIPILI/PDGFRA*-associated fusion gene

• Supportive therapy

Treatments include immediate therapy, definitive therapies (treatments directed at the disorder itself), and supportive therapies.

Immediate therapy: For patients with very severe eosinophilia, complications of hyperleukocytosis, or both (usually patients with eosinophilic leukemia), high-dose IV corticosteroids (eg, prednisone 1 mg/kg or equivalent) should be initiated as soon as possible. If the eosinophil count is much lower (eg, by ≥ 50%) after 24 h, corticosteroid dose can be repeated daily; if not, an alternative treatment (eg, vincristine, imatinib, leukapheresis) is begun.

Definitive therapy: Patients with the *FIPILI/PDGFRA*-associated fusion gene are usually treated with imatinib and, particularly if heart damage is suspected, corticosteroids. If imatinib is ineffective or poorly tolerated, another tyrosine kinase inhibitor (eg, dasatinib, nilotinib, sorafenib) can be used, or allogenic hematopoietic stem cell transplantation can be tried.

Patients without the *FIPILI/PDGFRA*-associated fusion gene, even if asymptomatic, are often given one dose of prednisone 60 mg (or 1 mg/kg) po to determine corticosteroid responsiveness (ie, a decrease in the eosinophil count). In patients with symptoms or organ damage, prednisone is continued at the same dose for 2 wk, then tapered. Patients without symptoms and organ damage are monitored for at least 6 mo for these complications. If corticosteroids cannot be easily tapered, a corticosteroid-sparing drug (eg,

hydroxyurea, interferon alfa) can be used.

Supportive therapy: Supportive drug therapy and surgery may be required for cardiac manifestations (eg, infiltrative cardiomyopathy, valvular lesions, heart failure). Thrombotic complications may require the use of antiplatelet drugs (eg, aspirin, clopidogrel, ticlopidine); anticoagulation is indicated if a left ventricular mural thrombus is present or if transient ischemic attacks persist despite use of aspirin.

Chapter 115. Histiocytic Syndromes

Introduction

The histiocytic syndromes are clinically heterogeneous disorders that result from an abnormal proliferation of histiocytes—either monocyte-macrophages (antigen-processing cells) or dendritic cells (antigen-presenting cells). Classifying these disorders is difficult (see Table 115-1) and has changed over time as an understanding of the biology of these cells has evolved.

Langerhans' Cell Histiocytosis

(See also p. 1963.)

Langerhans' cell histiocytosis (LCH) is a proliferation of dendritic mononuclear cells with infiltration into organs locally or diffusely. Most cases occur in children. Manifestations may include lung infiltrates; bone lesions; rashes; and hepatic, hematopoietic, and endocrine dysfunction. Diagnosis is based on biopsy. Factors predicting a poor prognosis include age < 2 yr and dissemination, particularly involving the hematopoietic

[**Table 115-1.** Some Histiocytic Syndromes]

system, liver, lungs, or a combination. Treatments include supportive measures and chemotherapy or local treatment with surgery or radiation therapy as indicated by the extent of disease.

LCH is a dendritic cell disorder. It can cause distinct clinical syndromes that have been historically described as eosinophilic granuloma, Hand-Schuller-Christian disease, and Letterer-Siwe disease. Because these syndromes may be varied manifestations of the same underlying disorder and because most patients with LCH have manifestations of more than one of these syndromes, the designations of the separate syndromes are now mostly of historical significance. Estimates of the prevalence of LCH vary widely (eg, from about 1:50,000 to 1:200,000).

In LCH, abnormally proliferating dendritic cells infiltrate one or more organs. Bone, skin, teeth, gingival tissue, ears, endocrine organs, lungs, liver, spleen, lymph nodes, and bone marrow may be involved. Organs may be affected by infiltration, causing dysfunction, or by compression from adjacent enlarged structures. In about half of patients, more than one organ is involved.

Symptoms and Signs

Symptoms and signs vary considerably depending on which organs are infiltrated. The syndromes are described by their historical designations, but few patients present with classic manifestations.

Eosinophilic granuloma: Solitary or multifocal eosinophilic granuloma (60 to 80% of LCH cases) occurs predominantly in older children and young adults, usually by age 30; incidence peaks between ages 5 and 10 yr. Lesions most frequently involve bone, often with pain, the inability to bear weight, or both and with overlying tender (sometimes warm) swelling.

Hand-Schuller-Christian disease: This syndrome (15 to 40% of LCH cases) occurs in children aged 2 to 5 yr and in some older children and adults. This systemic disorder classically involves the flat bones of the skull, ribs, pelvis, scapula, or a combination. Long bones and lumbosacral vertebrae are less frequently involved; the wrists, hands, knees, feet, and cervical vertebrae are rarely involved. In classic cases, patients have exophthalmos caused by orbital tumor mass. Rarely, vision loss or strabismus is caused by optic nerve or orbital muscle involvement. Tooth loss caused by apical and gingival infiltration is common in older patients.

Chronic otitis media and otitis externa due to involvement of the mastoid and petrous portions of the temporal bone with partial obstruction of the auditory canal are fairly common. Diabetes insipidus, the last component of the classic triad that includes flat bone involvement and exophthalmos, affects 5 to 50% of

patients, with higher percentages in children who have systemic disease and involvement of the orbit and skull. Up to 40% of children with systemic disease have short stature. Hyperprolactinemia and hypogonadism can result from hypothalamic infiltration.

Letterer-Siwe disease: This syndrome (10% of LCH cases), a systemic disorder, is the most severe form of LCH. Typically, a child < 2 yr presents with a scaly seborrheic, eczematoid, sometimes purpuric rash involving the scalp, ear canals, abdomen, and inter-triginous areas of the neck and face. Denuded skin may facilitate microbial invasion, leading to sepsis. Frequently, there is ear drainage, lymphadenopathy, hepatosplenomegaly, and, in severe cases, hepatic dysfunction with hypoproteinemia and diminished synthesis of clotting factors. Anorexia, irritability, failure to thrive, and pulmonary manifestations (eg, cough, tachypnea, pneumothorax) may also occur. Significant anemia and sometimes neutropenia occur; thrombocytopenia is of grave prognostic significance. Parents frequently report precocious eruption of teeth, when in fact the gums are receding to expose immature dentition. Patients may appear abused or neglected.

Diagnosis

• Biopsy

LCH is suspected in patients (particularly young patients) with unexplained pulmonary infiltrates, bone lesions, or ocular or craniofacial abnormalities; and in children < 2 yr with typical rashes or severe, unexplained multiorgan disease.

X-rays are often done because of presenting symptoms. Bone lesions are usually sharply marginated, and round or oval, with a beveled edge giving the appearance of depth. However, some lesions are radiographically indistinguishable from Ewing's sarcoma, osteogenic sarcoma, other benign and malignant conditions, or osteomyelitis.

Diagnosis is based on biopsy. Langerhans' cells are usually prominent, except in older lesions. These cells are identified by a pathologist experienced in the diagnosis of LCH according to their immunohistochemical characteristics, which include cell surface CD 1a and S-100. Once diagnosis is established, the extent of disease must be determined by appropriate imaging and laboratory studies.

Prognosis

Prognosis is good for patients with both of the following:

• Disease restricted to skin, lymph nodes, or bone

• Age > 2 yr

With treatment, almost all such patients survive.

Morbidity and mortality are increased in patients with multiorgan involvement, particularly those with

• Age < 2 yr

• Involvement of the hematopoietic system, liver, lungs, or spleen

With treatment, the overall survival rate for patients with multiorgan disease is about 80%. Death is more likely among at-risk patients who do not respond to initial therapy. Disease recurrence is common. A chronic remitting and exacerbating course may occur, particularly among adults.

Treatment

• Supportive care

• Sometimes hormone replacement therapy for hypopituitarism

• Chemotherapy for multiorgan involvement

• Sometimes surgery or radiation therapy (usually for single bone involvement)

Because these syndromes are rare and complex, patients are usually referred to institutions experienced in the treatment of LCH. General supportive care is essential and may include scrupulous hygiene to limit ear, cutaneous, and dental lesions. Debridement or resection of severely affected gingival tissue limits oral involvement. Seborrhea-like dermatitis of the scalp may diminish with use of a selenium-based shampoo twice/wk. If shampooing is ineffective, topical corticosteroids are used in small amounts and briefly in small areas.

Patients with systemic disease are monitored for potential chronic disabilities, such as cosmetic or functional orthopedic and cutaneous disorders and neurotoxicity as well as for psychologic problems that may require psychosocial support.

Many patients require hormone replacement for diabetes insipidus or other manifestations of hypopituitarism.

Chemotherapy is indicated for patients with multiorgan involvement. Protocols sponsored by the Histiocyte Society are used; treatment protocols vary according to the risk category. Almost all patients with a good response to therapy can stop treatment. Protocols for poor responders are under study.

Local surgery or radiation therapy is used for disease involving a single bone and, rarely, when multiple lesions or multiple bones are involved. Easily accessible lesions in noncritical locations undergo surgical curettage. Surgery should be avoided when it may result in significant cosmetic deformities, orthopedic deformities, or loss of function. Radiation therapy involving megavoltage equipment may be given to patients at risk of skeletal deformity, visual loss secondary to exophthalmos, pathologic fractures, vertebral collapse, and spinal cord injury or to patients with severe pain. Doses of radiation are considerably less than those used to treat cancer. Surgery and radiation therapy should be done by specialists experienced in treating LCH.

Patients with multiorgan disease that progresses despite standard therapy usually respond to more aggressive chemotherapy. Patients who do not respond to salvage chemotherapy may undergo bone marrow transplantation, experimental chemotherapy, or immunosuppressive or other immunomodulatory therapy.

Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon disorder causing immune dysfunction in infants and young children. Many patients have an underlying immune disorder, although in some patients the underlying disorder is not known. Manifestations may include lymphadenopathy, hepatosplenomegaly, fever, and neurologic abnormalities. Diagnosis is by specific clinical and testing (genetic) criteria. Treatment is usually with chemotherapy and, in refractory cases or in cases with a genetic cause, hematopoietic stem cell transplantation.

HLH is characterized by

• High levels of cytokines (eg, IL-1, IL-2; TNF-α; interferon [INF]-γ; soluble IL-6, IL-10, IL-12; granulocyte-macrophage colony stimulating factor [GM-CSF])

• Uncontrolled proliferation and activation of cytotoxic T cells, natural killer cells, and macrophages in multiple tissues

Certain aspects of immune function, such as natural killer cell and cytotoxic T-cell activity, are abnormal.

HLH is uncommon. It affects mostly infants < 18 mo. HLH can be

• Familial (primary)

• Acquired (secondary)

In both forms, genetic abnormalities, clinical manifestations, and outcomes tend to be similar. Acquired HLH can be associated with other immune disorders (eg, leukemias, lymphomas, SLE, RA, polyarteritis nodosa, sarcoidosis, progressive systemic sclerosis, Sjogren's syndrome, Kawasaki disease) and can occur in kidney or liver transplant recipients. Acquired HLH may be secondary to other disorders or to immunosuppressive regimens used to treat them or possibly to infections.

Symptoms and Signs

Common early manifestations include fever, hepatomegaly, splenomegaly, rash, lymphadenopathy, and neurologic abnormalities (eg, seizures, retinal hemorrhages, ataxia, altered consciousness or coma). Bone lesions may occur, and clinical manifestations may mimic child abuse.

Diagnosis

• Specific clinical and testing criteria

HLH is suspected in children with unexplained recurrent infections and typical laboratory abnormalities (cytopenias, coagulopathy, abnormal liver function test results, high serum ferritin levels) or with typical symptoms and signs.

Diagnosis requires the presence of > 5 of the following criteria:

• Fever (peak temperature of > 38.5°C for > 7 days)

• Splenomegaly (spleen palpable > 3 cm below costal margin)

• Cytopenia involving > 2 cell lines (Hb < 9 g/dL, absolute neutrophil count < 100/µL, platelets < 100,000/µL)

• Hypertriglyceridemia (fasting triglycerides > 2.0 mmol/L or > 3 standard deviations [SD] more than normal value for age) or hypofibrinogenemia (fibrinogen < 1.5 g/L or > 3 SD less than normal value for age)

• Hemophagocytosis (in biopsy samples of bone marrow, spleen, or lymph nodes)

• Low or absent natural killer cell activity

• Serum ferritin > 500 µg/L plus elevated soluble IL-2 (CD25) levels (> 2400 U/mL or very high for age)

Because some of these tests may not be widely available and HLH is uncommon, patients are usually referred to specialized centers for evaluation.

Treatment

• Hematopoietic stem cell transplantation and chemotherapy

Treatment should be started if the disorder is suspected, even if not all diagnostic criteria are fulfilled. Patients are usually treated by a pediatric hematologist and in a referral center experienced in treating patients with HLH. Depending on the presence of factors such as a family history of HLH, coexisting infections, and demonstrated immune system defects, treatment can involve combinations of hematopoietic stem cell transplantation, dexamethasone, cyclosporine, etoposide, and methotrexate.

Rosai-Dorfman Disease

(Sinus Histiocytosis With Massive Lymphadenopathy)

Rosai-Dorfman disease is a rare disorder characterized by accumulation of histiocytes and massive lymphadenopathy, particularly in the neck and head.

Rosai-Dorfman disease is most common among patients < 20 yr, particularly blacks. Cause is unknown.

The most common presenting symptoms are fever and massive, painless cervical adenopathy. Other nodal sites, including the mediastinum, retroperitoneum, axillae, and inguinal region, may be involved, as may the nasal cavity, salivary gland tissue, other regions of the head and neck, and CNS. Other manifestations may include lytic bone lesions, pulmonary nodules, and rash. The bone marrow and spleen are typically spared.

Laboratory testing usually shows leukocytosis, polyclonal hypergammaglobulinemia, hypochromic or normocytic anemia, and elevated ESR.

The disorder commonly resolves without treatment. Treatment is uncertain; chemotherapy has been tried.

Chapter 116. Myeloproliferative Disorders

Introduction

The myeloproliferative disorders are characterized by abnormal proliferation of one or more hematopoietic cell lines or connective tissue elements. They include

• Essential thrombocythemia

• Primary myelofibrosis

• Polycythemia vera

• Chronic myelocytic leukemia (see p. 1012)

Essential thrombocythemia, primary myelofibrosis, and polycythemia vera are Philadelphia chromosome-negative myeloproliferative disorders. Myeloproliferative disorders, particularly chronic myelocytic leukemia, sometimes lead to acute leukemia; some hematologists also classify hypereosinophilic syndrome and mastocytosis as myeloproliferative disorders. However, most experts argue that these disorders are sufficiently different and omit them.

Each disorder is identified according to its predominant feature or site of proliferation (see Table 116-1). Despite overlap, each disorder has a somewhat typical constellation of clinical features, laboratory findings, and course. Although proliferation of one cell line may dominate the clinical picture, each disorder is typically caused by clonal proliferation of a pluripotent stem cell, causing varying degrees of abnormal proliferation of RBC, WBC, and platelet precursors in the bone marrow. This abnormal clone does not, however, produce bone marrow fibroblasts, which can proliferate in polyclonal reactive fashion.

An abnormality of a tyrosine kinase called JAK2, involved in the bone marrow response to erythropoietin, contributes to the cause of polycythemia vera and causes a high proportion of cases of essential thrombocythemia and myelofibrosis.

[**Table 116-1.** Classification of Myeloproliferative Disorders]

Essential Thrombocythemia

(Essential Thrombocytosis; Primary Thrombocythemia)

Essential thrombocythemia (ET) is characterized by an increased platelet count, megakaryocytic hyperplasia, and a hemorrhagic or thrombotic tendency. Symptoms and signs may include weakness, headaches, paresthesias, bleeding, splenomegaly, and erythromelalgia with digital ischemia. Diagnosis is based on a platelet count > 450,000/µL, normal RBC mass or normal Hct in the presence of adequate iron stores, absence of myelofibrosis, the Philadelphia chromosome (or *BCR-ABL* rearrangement), and any other disorder that could cause thrombocytosis. Treatment is controversial but may include aspirin. Patients > 60 yr and those with previous thromboses and transient ischemic attacks require cytotoxic drugs to decrease risk of thromboses. Data suggest that risk of thrombosis does not correlate with platelet count, although anecdotal experience suggests otherwise.

Pathophysiology

ET is a typically clonal abnormality of a multipotent hematopoietic stem cell. However, some women who fulfill diagnostic criteria for ET have polyclonal hematopoiesis. ET usually occurs with bimodal peaks of between ages 50 and 70 yr and a separate peak among young females.

Platelet production is increased. Platelet survival is usually normal, although it may decrease due to splenic sequestration and in patients with erythromelalgia with digital ischemia.

In elderly patients with atherosclerosis, increased platelets may lead to serious bleeding or, more commonly, thrombosis. Thrombosis is the major cause of morbidity and mortality. Recent studies indicate that an elevated leukocyte count is a major independent risk factor for thromboses. Although anecdotally (and intuitively), elevated platelet count may increase the risk of thrombosis, one study found an inverse relationship between absolute platelet count and thrombotic risk. Bleeding is more likely with extreme thrombocytosis (ie, > 1.5 million platelets/µL) due to an acquired von Willebrand's factor deficiency.

Symptoms and Signs

Common symptoms are

• Weakness

• Hemorrhage

• Gout

• Ocular migraines

• Paresthesias of the hands and feet

Thrombosis may cause symptoms in the affected site (eg, neurologic deficits with stroke or transient ischemic attack, leg pain, swelling or both with lower extremity thrombosis, chest pain and dyspnea with pulmonary embolism). Bleeding is usually mild and manifests as epistaxis, easy bruisability, or GI bleeding. Digital ischemia may occur, and splenomegaly (usually not extending > 3 cm below the left costal margin) occurs in < 50% of patients. Hepatomegaly may rarely occur. In pregnant patients, thrombosis may cause recurrent spontaneous abortions.

Diagnosis

• CBC and peripheral blood smear

• Cytogenetic studies

• Possibly bone marrow examination

ET should be considered in patients in whom common reactive causes (see p. 999) are excluded. If ET is suspected, CBC, peripheral blood smear, and cytogenetic studies, including Philadelphia chromosome or *BCR-ABL* assay, should be done. Some authorities recommend bone marrow examination, but although classic ET morphologic abnormalities have been described, the diagnostic value of bone marrow examination is not established. The platelet count can be > 1,000,000/µL but may be as low as 450,000/µL. Platelet count may decrease spontaneously during pregnancy. The peripheral smear may show platelet aggregates, giant platelets, and megakaryocyte fragments. The bone marrow shows megakaryocytic hyperplasia, with an abundance of platelets being released. Bone marrow iron is present. To distinguish from other myeloproliferative disorders that produce thrombocytosis, the diagnosis of ET requires a normal Hct, MCV, and iron studies; absence of the Philadelphia chromosome and *BCR-ABL* translocation; and absence of teardrop-shaped RBCs; there may be significant increase in bone marrow fibrosis (present in idiopathic myelofibrosis). The *JAK2V617F* mutation occurs in about 50% of patients, and a small minority of ET patients has acquired somatic thrombopoietin receptor gene mutations (*c-mpl*).

Prognosis

Life expectancy is near normal. Although symptoms are common, the course of the disease is often benign. Serious arterial and venous thrombotic complications are rare but can be life-threatening. Leukemic transformation occurs in < 2% of patients but may increase after exposure to cytotoxic therapy, especially alkylating agents.

Treatment

• Aspirin

• Platelet-lowering drugs (eg, hydroxyurea, anagrelide)

• Rarely plateletpheresis

For mild vasomotor symptoms (eg, headache, mild digital ischemia, erythromelalgia) and to decrease the risk of thrombosis in low-risk patients, aspirin 81 mg po once/day may be sufficient. Also, most pregnant patients are given aspirin. Use in low-risk patients is acceptable but not data-proven.

Because prognosis is often good, potentially toxic drugs that lower the platelet count should be used sparingly. Generally agreed indications for such therapy are

• Previous thromboses or transient ischemic attack

• Age > 60 yr

Other indications are controversial. Patients with significant bleeding and extreme thrombocytosis (high-risk patients) may need therapy to lower the platelet count. It is unclear whether asymptomatic patients < 60 yr need platelet-lowering drugs. Myelosuppressive drugs to lower platelet count include anagrelide, interferon alfa-2b, and hydroxyurea (sometimes with low-dose aspirin). Hydroxyurea is generally considered the drug of choice, although some clinicians prefer anagrelide. Because anagrelide and hydroxyurea cross the placenta, they are not used during pregnancy; interferon alfa-2b can be used in pregnant women when necessary.

Dosage and monitoring are described in the treatment of polycythemia vera (see p. 1000). The conventional aim of therapy is a platelet count < 450,000/µL without significant clinical toxicity or suppression of other bone marrow elements; however, this goal needs to be reevaluated in view of recent data suggesting an inverse relationship between platelet count and thrombotic risk.

Plateletpheresis has been used in rare patients with serious hemorrhage and recurrent thrombosis or before emergency surgery to immediately reduce the platelet count; this procedure, however, is rarely necessary. Due to the long half-life of platelets (7 days), hydroxyurea and anagrelide do not provide an immediate effect.

Thrombocytosis

(Secondary Thrombocythemia)

Thrombocytosis can develop secondary to

• Chronic inflammatory disorders, eg, RA, inflammatory bowel disease, TB, sarcoidosis, Wegener's granulomatosis

• Acute infection

• Hemorrhage

• Iron deficiency

• Hemolysis

• Cancer (particularly Hodgkin lymphoma, non-Hodgkin lymphoma)

• Splenectomy

• Myeloproliferative and hematologic disorders (eg, polycythemia vera, chronic myelocytic leukemia,

sideroblastic anemia, myelodysplasia [5q- syndrome], idiopathic myelodysplasia)

There are also congenital familial thrombocytoses such as those due to thrombopoietin and thrombopoietin receptor gene mutations.

Platelet function is usually normal. Unlike ET, thrombocytosis does not increase the risk of thrombotic or hemorrhagic complications unless patients have severe arterial disease or prolonged immobility. With secondary thrombocytosis, the platelet count is usually < 1,000,000/µL, and the cause may be obvious from the history and physical examination (perhaps with confirmatory testing). CBC and peripheral blood smear should help suggest iron deficiency or hemolysis. If a cause is not obvious, evaluation for a myeloproliferative disorder should be considered.

Treatment of the underlying disorder usually returns the platelet count to normal.

Primary Myelofibrosis

(Agnogenic Myeloid Metaplasia; Myelofibrosis with Myeloid Metaplasia)

Primary myelofibrosis (PMF) is a chronic, usually idiopathic disorder characterized by bone marrow fibrosis, splenomegaly, and anemia with immature and teardrop-shaped RBCs. Diagnosis requires bone marrow examination and exclusion of other conditions that can cause myelofibrosis (secondary myelofibrosis). Treatment is usually supportive.

Pathophysiology

Myelofibrosis is excessive bone marrow fibrosis and loss of hematopoietic cells, with subsequent marked increase in extramedullary hematopoiesis (primarily in the liver and spleen, which enlarge significantly). Myelofibrosis may be primary or secondary to a number of hematologic, malignant, and nonmalignant conditions (see
Table 116-2).

PMF is more common than secondary myelofibrosis and results from neoplastic transformation of a multipotent bone marrow stem cell. These PMF progeny cells stimulate bone marrow fibroblasts (which are not part of the neoplastic transformation) to secrete excessive collagen. The peak incidence of PMF is between 50 and 70 yr.

In PMF, large numbers of nucleated RBCs (normoblasts) and granulocytes are released into the circulation (leukoerythroblastosis). Serum LDH level is often elevated. Bone marrow failure eventually occurs, with consequent anemia and thrombocytopenia. Rapidly

[**Table 116-2.** Conditions Associated with Myelofibrosis]

progressive, chemotherapy-incurable acute leukemia develops in about 10% of patients.

Malignant or acute myelofibrosis, an unusual variant, has a more rapidly progressive downhill course; this variant may actually be a true megakaryocytic leukemia.

Symptoms and Signs

In many patients, myelofibrosis is asymptomatic. Other patients have symptoms of anemia, splenomegaly, or, in later stages, general malaise, weight loss, fever, or splenic infarction. Hepatomegaly occurs in a significant proportion of patients. Lymphadenopathy is rare.

Diagnosis

• CBC and peripheral blood smear

• Bone marrow examination

PMF should be suspected in patients with splenomegaly, splenic infarction, anemia, or unexplained elevations in LDH. If the disorder is suspected, CBC should be done and peripheral blood morphology and bone marrow should be examined, including cytogenetic testing. If myelofibrosis is detected on bone marrow examination (eg, by increased fibroblasts and collagen as detected by reticulin staining, osteosclerosis), other disorders associated with myelofibrosis (see Table 116-2) should be excluded by appropriate clinical and laboratory evaluation.

Anemia is typically present and usually increases over time. Blood cell morphology is variable. RBCs are poikilocytic. Reticulocytosis and polychromatophilia may be present; teardrop-shaped RBCs (dacryocytes) are characteristic morphologic features. Nucleated RBCs and neutrophil precursors are typically present in peripheral blood. WBC counts are usually increased but are highly variable; a low WBC count tends to indicate a poor prognosis. Neutrophils are usually immature, and myeloblasts may be present, even in the absence of acute leukemia. Platelet counts initially may be high, normal, or decreased; however, thrombocytopenia tends to supervene as the disorder progresses.

If diagnosis is difficult, CD34+ cell count on peripheral blood can be done. Levels are much higher in patients with PMF.

Bone marrow aspiration is usually dry. Because demonstration of bone marrow fibrosis is required and fibrosis may not be uniformly distributed, biopsy should be repeated at a different site if the first biopsy is nondiagnostic.

Prognosis

The median survival is 5 yr from onset, but variation is wide; some patients have a rapidly progressing disorder with short survival and some have a delay in initial diagnosis. Unfavorable prognostic markers include Hb < 10 g/dL, history of transfusions, leukocytosis and leukopenia, and platelet count < 100,000/µL. Patients in the least favorable risk group usually survive < 1 yr. No treatment reverses or controls the underlying process except for allogeneic stem cell transplant.

Treatment

• Symptomatic therapy

• Sometimes allogeneic stem cell transplantation

Treatment is directed at symptoms and complications. Androgens, splenectomy, chemotherapy, and splenic embolization and radiation therapy have been used for palliation. For patients with low erythropoietin levels relative to the degree of anemia, erythropoietin may increase Hct sufficiently; otherwise, RBC transfusion may be necessary. For younger patients with advanced disease, allogeneic stem cell transplantation should be considered. Nonmyeloablative allogeneic stem cell transplantation has been successfully used even in older patients; however, it is usually limited to patients < 65 yr.

Inhibitors of the JAK pathway appear to have a significant effect on splenomegaly and abnormal peripheral hematologic abnormalities. These drugs are in early trials.

Polycythemia Vera

(Primary Polycythemia)

Polycythemia vera (PV) is an idiopathic chronic myeloproliferative disorder characterized by an increase in RBC mass, which often manifests as an increased Hct. There is an increased risk of thrombosis and, rarely, acute leukemia and myelofibrotic transformation. Hepatosplenomegaly may also occur. Diagnosis is made by CBC, testing for *JAK2* mutations, and clinical criteria. Treatment involves low-dose aspirin for all patients and myelosuppressive drugs for high-risk patients; phlebotomy, once standard, is now controversial.

PV is the most common of the myeloproliferative disorders; incidence in the US is estimated to be 1.9/100,000, with incidence increasing with age. PV may be slightly more common in men. The mean age at diagnosis is around 60 yr. PV is very rare in children.

Pathophysiology

PV involves increased production of all cell lines, including RBCs, WBCs, and platelets. Thus, PV is sometimes called a panmyelosis because of elevations of all 3 peripheral blood components. Increased production confined to the RBC line is termed erythrocytosis; erythrocytosis may occur with PV but is more commonly due to other causes (secondary erythrocytosis—see p. 1003). In PV, RBC production proceeds independently of erythropoietin levels.

Extramedullary hematopoiesis may occur in the spleen, liver, and other sites that have the potential for blood cell formation. Peripheral blood cell turnover increases. Eventually, progression to a spent-phase may occur, with a phenotype indistinguishable from primary myelofibrosis. Transformation to acute leukemia is rare, although the risk is increased with exposure to alkylating agents and radioactive phosphorus, which should only be used rarely, if ever.

Complications: In PV, blood volume expands and hyperviscosity develops. Patients are prone to develop thrombosis. Thrombosis can occur in most blood vessels, resulting in stroke, transient ischemic attacks, deep venous thrombosis, MI, retinal artery or vein occlusion, splenic infarction (often with a friction rub), or Budd-Chiari syndrome (see p. 261). Previously, most experts believed hyperviscosity was the predisposing factor for thrombosis. Newer studies suggest that risk of thrombosis may be primarily related to the degree of leukocytosis. However, this hypothesis has yet to be confirmed in dedicated, prospective trials.

Platelets may function abnormally, predisposing to increased bleeding. Increased cell turnover may cause hyperuricemia, increasing the risk of gout and urate kidney stones.

Genetic basis: Clonal hematopoiesis is a hallmark of PV, suggesting that a mutation of hematopoietic stem cells is the cause of proliferation. The *JAK2 V617F* mutation (or one of several other rarer *JAK2* mutations) is present in virtually all patients with PV. However, one or more other disease-initiating mutations almost certainly exist. These mutations lead to sustained activation of the JAK2 protein, which causes excess cell production, independent of erythropoietin levels.

Symptoms and Signs

PV itself is often asymptomatic. Occasionally, increased red cell volume and viscosity produce weakness, headache, light-headedness, visual disturbances, fatigue, and dyspnea. Pruritus often occurs, particularly after a hot bath. The face may be red and the retinal veins engorged. The palms and feet may be red, warm, and painful, sometimes with digital ischemia (erythromelalgia). Hepatomegaly is common, and > 75% of patients have splenomegaly (which may be massive).

Thrombosis may cause symptoms in the affected site (eg, neurologic deficits with stroke or transient ischemic attack, leg pain, swelling or both with lower extremity thrombosis, unilateral vision loss with retinal vascular occlusion).

Bleeding (typically GI) occurs in about 10% of patients.

Hypermetabolism can cause low-grade fevers and weight loss and suggests progression to spent-phase polycythemia, which is clinically indistinguishable from primary myelofibrosis.

Diagnosis

- CBC
- Testing for *JAK2* mutations

• Sometimes bone marrow examination and serum erythropoietin level

• Use of WHO criteria

PV is often first suspected because of an abnormal CBC (eg, Hb > 18.5 g/dL in men or > 16.5 g/dL in women), but it must be considered in patients with suggestive symptoms, particularly Budd-Chiari syndrome (however, some patients develop Budd-Chiari syndrome before the Hct increases). Neutrophils and platelets are often, but not invariably, increased; in patients with only elevated Hb, PV may be present, but secondary erythrocytosis, a more common cause of elevated Hb, must first be considered (see p. 1003). PV should also be considered in the rare patient with a normal Hb level but microcytosis and evidence of iron deficiency; this combination of findings can occur with iron-limited hematopoiesis, which is a hallmark of some cases of PV.

New WHO criteria for diagnosis have been established (see Table 116-3). Thus, patients suspected of having PV typically should have testing for *JAK2* mutations; bone marrow examination is not always necessary.

When done, bone marrow typically shows panmyelosis, large and clumped megakaryocytes, and sometimes reticulin fibers. However, no bone marrow findings absolutely differentiate between PV and other disorders of excessive erythrocytosis, such as congenital familial polycythemia.

[**Table 116-3.** WHO Criteria for Diagnosis of Polycythemia Vera*]

Patients with PV typically have low or low-normal serum erythropoietin levels. Elevated levels suggest secondary erythrocytosis.

Sometimes in vitro testing for endogenous erythroid colony formation is done (erythroid progenitors from peripheral blood or bone marrow from patients with PV, unlike those from healthy people, can form erythroid cells in culture without the addition of erythropoietin).

RBC mass determination with chromium-labeled RBCs can help differentiate between true and relative polycythemia and can also help to differentiate between PV and other myeloproliferative disorders. However, this test is technically difficult and is usually not done due to its limited availability and the fact it has been standardized only at sea level.

Nonspecific laboratory abnormalities that may occur in PV include elevated vitamin B_{12} and B_{12}-binding capacity, hyperuricemia and hyperuricosuria (present in ≥ 30% of patients), increased expression of *PRV-1* gene in leukocytes, and decreased expression of C-mpl (the receptor for thrombopoietin) in megakaryocytes and platelets. These tests are not needed for diagnosis.

Prognosis

Generally, PV is associated with a shortened life span. Median survival for all patients is around 8 to 15 yr, although many patients live much longer. Thrombosis is the most common cause of death, followed by complications of myelofibrosis and development of leukemia.

Treatment

• Aspirin therapy

• Possibly phlebotomy

• Possibly myelosuppressive therapy

Because PV is the only form of erythrocytosis for which myelosuppressive therapy may be indicated, accurate diagnosis is critical. Therapy must be individualized according to age, sex, medical status, clinical manifestations, and hematologic findings. Patients are classified as high-risk or low-risk. High-risk patients are > 60 yr and have a history of thrombosis or transient ischemic attacks or both.

Aspirin: Aspirin (81 to 100 mg po once/day) reduces the incidence of thrombotic complications. Thus, patients undergoing phlebotomy alone or phlebotomy and myelosuppression should be given aspirin unless contraindicated. Higher doses of aspirin are associated with an unacceptably increased risk of bleeding.

Phlebotomy: Phlebotomy has been the mainstay of therapy for high- and low-risk patients because experts believed it decreased the risk of thrombosis. However, use of phlebotomy is now controversial because recent studies suggest that the Hct level may not correlate with risk of thrombosis, and some clinicians no longer adhere to the strict phlebotomy guidelines. However, this issue requires further study, and phlebotomy may still be considered for any patient. In a minority of patients with symptomatic rubor and hyperviscosity symptoms, phlebotomy can be therapeutic. Common thresholds for phlebotomy are Hct > 45% in men and > 42% in women. Initially, 300 to 500 mL of blood are removed every other day. Less blood is removed (ie, 200 to 300 mL twice/wk) from elderly patients and from patients with cardiac or cerebrovascular disorders. Once the Hct is below the threshold value, it is checked monthly and maintained at this level by additional phlebotomies as needed. If necessary, intravascular volume can be maintained with crystalloid or colloid solutions.

Myelosuppressive therapy: Myelosuppressive therapy is indicated for high-risk patients.

Radioactive phosphorus (^{32}P) has long been used as a treatment for PV. It has a success rate of 80 to 90%. Remission may last 6 mo to several years. Radioactive phosphorus is well tolerated and requires fewer follow-up visits once the disorder is controlled. However, radioactive phosphorus is associated with an increased incidence of acute leukemic transformation, and the leukemia that develops after this therapy is often resistant to induction chemotherapy and is never curable. Thus, use of radioactive phosphorus requires careful patient selection (eg, used only for patients who are expected to die of other disorders within 5 yr). It should be used rarely; many clinicians do not use it at all.

Hydroxyurea, which inhibits the enzyme ribonucleoside diphosphate reductase, is also used to achieve myelosuppression. It has not been clearly shown to be leukemogenic; however, the possibility of leukemic conversion, although small, does exist. Hydroxyurea is started at a dose of 500 to 1000 mg po once/day. Patients are monitored with a weekly CBC. When a steady state is achieved, the interval between CBCs is lengthened to 2 wk and then to 4 wk. If the WBC count falls to < 4000/µL or the platelet count to < 100,000/µL, hydroxyurea is withheld and reinstituted at 50% of the dose when those values normalize. It is reasonable to titrate the hydroxyurea dose to achieve a near-normal Hct, although there is no evidence that titration is beneficial. It is likely that normalization of the WBC count is more important, but this theory has not been demonstrated prospectively. There is no evidence that normalization of the platelet count is necessary, and some clinicians do not increase the hydroxyurea dose as long as the platelet count is < 1.5 million/µL. Acute toxicity is infrequent; occasionally patients develop a rash, GI symptoms, fever, nail changes, and skin ulcers, which may require stopping hydroxyurea.

Interferon alfa-2b has been used if hydroxyurea does not control blood counts or is not tolerated. However, pegylated interferon alfa-2b is usually well tolerated. This drug affects the disease at the molecular level with relatively low toxicity.

Alkylating agents are leukemogenic and should be avoided.

Several inhibitors of the JAK2 pathway are currently in clinical trials, primarily in patients with advanced myelofibrosis.

Treatment of complications: Hyperuricemia should be treated with allopurinol 300 mg po once/day if it causes symptoms or if patients are receiving simultaneous myelosuppressive therapy. Pruritus may be managed with antihistamines but is often difficult to control; myelosuppression often is most effective. Cholestyramine 4 g po tid, cyproheptadine 4 mg po tid to qid, cimetidine 300 mg po qid, or paroxetine 20 to 40 mg po once/day may be successful. After bathing, the skin should be dried gently. Aspirin relieves symptoms of erythromelalgia; higher doses may be required but clearly increase the risk of hemorrhage.

Secondary Erythrocytosis

(Secondary Polycythemia)

Secondary erythrocytosis is erythrocytosis that develops secondary to circulating erythropoiesis-stimulating substances.

In secondary erythrocytosis, only the RBC line is increased.

Common causes of secondary erythrocytosis include

• Smoking

• Chronic arterial hypoxemia

• Tumors (tumor-associated erythrocytosis)

Less common causes include certain congenital disorders such as

• High O_2-affinity hemoglobinopathies

• Erythropoietin receptor mutations

• Chuvash polycythemia (in which a mutation in the *VHL* gene affects the hypoxia-sensing pathway)

• Proline hydroxylase 2 and hypoxia-inducible factor 2 *(HIF-2)* α mutations

Spurious erythrocytosis may occur with hemoconcentration (eg, from burns, diarrhea, diuretics).

In patients who smoke, reversible erythrocytosis results mainly from tissue hypoxia due to elevation of blood carboxyhemoglobin concentration; levels often normalize with smoking cessation.

Patients with chronic hypoxemia (arterial Hb O_2 concentration < 92%), typically due to lung disease, right-to-left intracardiac shunts, renal transplantation, prolonged exposure to high altitudes (see p. 3275), or hypoventilation syndromes, often develop erythrocytosis. The primary treatment is to alleviate the underlying condition, but O_2 therapy may help, and some degree of phlebotomy may decrease viscosity and alleviate symptoms. Because in some cases the elevated Hct is physiologic, phlebotomy may cause harm because it decreases tissue oxygenation.

Tumor-associated erythrocytosis can occur when renal tumors, cysts, hepatomas, cerebellar hemangioblastomas, or uterine leiomyomas secrete erythropoietin. Removal of the lesion may be curative.

High O_2-affinity hemoglobinopathies are very rare. This diagnosis is suggested by a family history of erythrocytosis; it is established by measuring the P_{50} (the partial pressure of O_2 at which Hb becomes 50% saturated) and, if possible, determining the complete oxyhemoglobin dissociation curve. Standard Hb electrophoresis may be normal and cannot reliably exclude this cause of erythrocytosis.

Evaluation: Tests done when erythrocytosis is present include

• Arterial O_2 saturation

• Serum erythropoietin levels

• P_{50}

A low or low-normal serum erythropoietin level suggests PV. Patients with hypoxia-induced erythrocytosis have an elevated level or inappropriately normal level for their elevated Hct. Patients with tumor-

associated erythrocytosis typically have elevated erythropoietin levels. Patients with elevated erythropoietin levels or microscopic hematuria should undergo abdominal imaging, CNS imaging, or both to seek a renal lesion or other tumor source of erythropoietin.

P_{50} measures the affinity of Hb for O_2; a normal result excludes a high-affinity Hb (a familial abnormality) as the cause of erythrocytosis.

Chapter 117. Leukemias

Introduction

The leukemias are cancers of the WBCs involving bone marrow, circulating WBCs, and organs such as the spleen and lymph nodes.

Etiology

Risk of developing most leukemias increases with

- History of exposure to ionizing radiation (eg, post-atom bomb in Nagasaki and Hiroshima) or to chemicals (eg, benzene)
- Prior treatment with certain antineoplastic drugs, particularly procarbazine, nitrosureas (cyclophosphamide, melphalan), and epipodophyllotoxins (etoposide, teniposide)
- Infection with a virus (eg, human T-lymphotrophic virus 1 and 2, Epstein-Barr virus)
- Chromosomal translocations
- Preexisting conditions, including immunodeficiency disorders, chronic myeloproliferative disorders, and chromosomal disorders (eg, Fanconi's anemia, Bloom syndrome, ataxia-telangiectasia, Down syndrome, infantile X-linked agammaglobulinemia)

Pathophysiology

Malignant transformation usually occurs at the pluripotent stem cell level, although it sometimes involves a committed stem cell with more limited capacity for differentiation. Abnormal proliferation, clonal expansion, and diminished apoptosis (programmed cell death) lead to replacement of normal blood elements with malignant cells.

Manifestations of leukemia are due to suppression of normal blood cell formation and organ infiltration by leukemic cells. Inhibitory factors produced by leukemic cells and replacement of marrow space may suppress normal hematopoiesis, with ensuing anemia, thrombocytopenia, and granulocytopenia. Organ infiltration results in enlargement of the liver, spleen, and lymph nodes, with occasional kidney and gonadal involvement. Meningeal infiltration results in clinical features associated with increasing intracranial pressure (eg, cranial nerve palsies).

Classification

Leukemias were originally termed acute or chronic based on life expectancy but now are classified according to cellular maturity.

Acute leukemias consist of predominantly immature, poorly differentiated cells (usually blast forms). Acute leukemias are divided into lymphocytic (ALL) and myelocytic (AML) types, which may be further subdivided by the French-American-British (FAB) classification (see Table 117-1).

Chronic leukemias have more mature cells than do acute leukemias. Chronic leukemias are described as lymphocytic (CLL) or myelocytic (CML—see Table 117-2).

Myelodysplastic syndromes involve progressive bone marrow failure but with an insufficient proportion of blast cells (< 30%) for making a definite diagnosis of AML; 40 to 60% of cases evolve into AML.

A **leukemoid reaction** is marked granulocytic leukocytosis (ie, WBC > 30,000/µL) produced by normal bone marrow in response to systemic infection or cancer. Although not a neoplastic disorder, a leukemoid

reaction with a very high WBC count may require testing to distinguish it from CML (see p. 1012).

Acute Leukemia

Acute leukemia occurs when a hematopoietic stem cell undergoes malignant transformation into a primitive, undifferentiated cell with abnormal longevity. These lymphocytes (acute lymphocytic leukemia [ALL]) or myeloid cells (acute myelocytic leukemia [AML]) proliferate abnormally, replacing normal marrow tissue and hematopoietic cells and inducing anemia, thrombocytopenia, and granulocytopenia. Because they are blood-borne, they can infiltrate various organs and sites, including the liver, spleen, lymph nodes, CNS, kidneys, and gonads.

Symptoms and Signs

Symptoms have usually been present for only days to weeks before diagnosis. Disrupted hematopoiesis leads to the most common presenting symptoms (anemia, infection, easy bruising and bleeding). Other presenting symptoms and signs are usually nonspecific (eg, pallor, fatigue, fever, malaise, weight loss, tachycardia, chest pain) and are attributable to anemia and a hypermetabolic state. The cause of fever often is not found, although granulocytopenia may lead to a rapidly progressing and potentially life-threatening bacterial infection. Bleeding is usually manifested by petechiae, easy bruising, epistaxis, bleeding gums, or menstrual irregularity. Hematuria and GI bleeding are uncommon. Bone marrow and periosteal infiltration may cause bone and joint pain, especially in children with ALL. Initial CNS involvement or leukemic meningitis (manifesting as headaches, vomiting, irritability, cranial nerve palsies, seizures, and papilledema) is uncommon. Extramedullary infiltration by leukemic cells may cause

[**Table 117-1.** French-American-British (FAB) Classification of Acute Leukemias]

[**Table 117-2.** Findings at Diagnosis in the Most Common Leukemias]

lymphadenopathy, splenomegaly, hepatomegaly, and leukemia cutis (a raised, nonpruritic rash).

Diagnosis

• CBC and peripheral blood smear

• Bone marrow examination

• Histochemical studies, cytogenetics, immunophenotyping, and molecular biology studies

• Imaging

CBC and peripheral smear are the first tests done; pancytopenia and peripheral blasts suggest acute leukemia. Blast cells in the peripheral smear may approach 90%, unless the WBC count is markedly decreased. Although the diagnosis can usually be made from the peripheral smear, bone marrow examination (aspiration or needle biopsy) should always be done. Blast cells in the bone marrow are between 20 and 95%. Aplastic anemia, viral infections such as infectious mononucleosis, and vitamin B_{12} and folate deficiency should be considered in the differential diagnosis of severe pancytopenia. Leukemoid reactions to infectious disease (such as TB) can manifest as high blast counts.

Histochemical studies, cytogenetics, immunophenotyping, and molecular biology studies help distinguish the blasts of ALL from those of AML or other disease processes. Specific B-cell, T-cell, and myeloid-antigen monoclonal antibodies, together with flow cytometry, are very helpful in classifying ALL vs AML, which is critical for treatment.

Other laboratory findings may include hyperuricemia, hyperphosphatemia, hyperkalemia or hypokalemia, elevated serum hepatic transaminases or LDH, hypoglycemia, and hypoxia. Lumbar puncture and head CT scan are done in patients with CNS symptoms, B-cell ALL, high WBC count, or high LDH. Chest x-ray is done; if a mediastinal mass is present, CT may be done. CT, MRI, or abdominal ultrasonography may help assess splenomegaly or leukemia infiltration of other organs.

Prognosis

Cure is a realistic goal for both ALL and AML, especially in younger patients. Prognosis is worse in infants and the elderly and in those with hepatic or renal dysfunction, CNS involvement, myelodysplasia, or a high WBC count (> 25,000/µL). Survival in untreated acute leukemia generally is 3 to 6 mo. Prognosis varies according to karyotype.

Treatment

• Chemotherapy

• Supportive care

The goal of treatment is complete remission, including resolution of abnormal clinical features, restoration of normal blood counts and normal hematopoiesis with < 5% blast cells, and elimination of the leukemic clone. Although basic principles in treating ALL and AML are similar, the drug regimens differ. The complex nature of patients' clinical situations and the available treatment protocols necessitate an experienced team. Whenever possible, patients should be treated at specialized medical centers, particularly during critical phases (eg, remission induction).

Supportive care: Supportive care is similar in the acute leukemias and may include

• Transfusions

• Antibiotics or antifungal drugs

• Hydration and urine alkalinization

• Psychologic support

Transfusions of platelets, RBCs, and granulocytes are administered as needed to patients with bleeding, anemia, and neutropenia, respectively. Prophylactic platelet transfusion is done when platelets fall to < 10,000/µL; a higher threshold (20,000/µL) is used for patients with the triad of fever, disseminated intravascular coagulation, and mucositis secondary to chemotherapy. Anemia (Hb < 8 g/dL) is treated with packed RBC transfusions. Granulocyte transfusions may help neutropenic patients with gram-negative or other serious sepsis but have no proven benefit as prophylaxis.

Antimicrobials are often needed because infections are serious in neutropenic, immunosuppressed patients and can progress quickly without the usual clinical evidence. After appropriate studies and cultures have been done, both febrile and afebrile patients with neutrophil counts < 500/µL should begin broad-spectrum bactericidal antibiotic treatment that is effective against gram-positive and gram-negative organisms (eg, ceftazidime, imipenem, cilastatin). Fungal infections, especially pneumonias, are becoming more common and are difficult to diagnose; empiric antifungal drugs should be given if antibacterial therapy is not effective within 72 h. In patients with refractory pneumonitis, *Pneumocystis jirovecii* infection or a viral infection should be suspected and confirmed by bronchoscopy and bronchoalveolar lavage and treated appropriately. Empiric therapy with trimethoprim/sulfamethoxazole (TMP/SMX), amphotericin B, and acyclovir or other analogs, often with granulocyte transfusions, is often necessary. In patients with drug-induced immunosuppression at risk of opportunistic infections, TMP/SMX is given to prevent *P. jirovecii* pneumonia.

Hydration (twice the daily maintenance volume), urine alkalinization (pH 7 to 8), and electrolyte monitoring can prevent the hyperuricemia, hyperphosphatemia, and hyperkalemia (tumor lysis syndrome —see p. 1075) caused by the rapid lysis of leukemic cells during initial therapy (particularly in ALL). Hyperuricemia can be minimized by giving allopurinol (a xanthine oxidase inhibitor) or rasburicase (a recombinant urate-oxidase enzyme) before starting chemotherapy to reduce the conversion of xanthine to uric acid.

Psychologic support may help patients and their families weather the shock of illness and the rigors of treatment for a potentially life-threatening condition.

Acute Lymphocytic Leukemia

(Acute Lymphoblastic Leukemia)

ALL is the most common pediatric cancer; it also strikes adults of all ages. Malignant transformation and uncontrolled proliferation of an abnormally differentiated, long-lived hematopoietic progenitor cell results in a high circulating number of blasts, replacement of normal marrow by malignant cells, and the potential for leukemic infiltration of the CNS and abdominal organs. Symptoms include fatigue, pallor, infection, and easy bruising and bleeding. Examination of peripheral smear and bone marrow is usually diagnostic. Treatment typically includes combination chemotherapy to achieve remission, intrathecal chemotherapy for CNS prophylaxis and/or cerebral irradiation for intracerebral leukemic infiltration, consolidation chemotherapy with or without stem cell transplantation, and maintenance chemotherapy for 1 to 3 yr to avoid relapse.

Two thirds of all ALL cases occur in children, with a peak incidence at age 2 to 5 yr; ALL is the most common cancer in children and the 2nd most common cause of death in children < 15 yr. A 2nd rise in incidence occurs after age 45.

Prognosis

Prognostic factors help determine treatment protocol and intensity.

Favorable prognostic factors are

- Age 3 to 7 yr
- WBC count < 25,000/μL
- French-American-British (FAB) L1 morphology
- Leukemic cell karyotype with > 50 chromosomes and t(12;21)
- No CNS disease at diagnosis

Unfavorable factors are

- A leukemic cell karyotype with chromosomes that are normal in number but abnormal in morphology (pseudodiploid)
- Presence of the Philadelphia (Ph) chromosome t(9;22)
- Increased age in adults
- B-cell immunophenotype with surface or cytoplasmic immunoglobulin

Regardless of prognostic factors, the likelihood of initial remission is ≥ 95% in children and 70 to 90% in adults. About 75% of children and 30 to 40% of adults have continuous disease-free survival for 5 yr and appear cured. Imatinib improves outcome in patients with Ph chromosome-positive ALL. Most investigatory protocols select patients with poor prognostic factors for more intense therapy, because the increased risk of and toxicity from treatment are outweighed by the greater risk of treatment failure leading to death.

Treatment

• Chemotherapy

• Sometimes stem cell transplantation or radiation therapy

The 4 general phases of chemotherapy for ALL include

• Remission induction

• CNS prophylaxis

• Postremission consolidation or intensification

• Maintenance

Induction therapy: The goal is to induce remission. Several regimens emphasize early introduction of an intensive multidrug regimen. Remission can be induced with daily oral prednisone and weekly IV vincristine with the addition of an anthracycline or asparaginase. Other drugs and combinations that may be introduced early in treatment are cytarabine and etoposide as well as cyclophosphamide. In some regimens, intermediate-dose or high-dose IV methotrexate is given with leucovorin rescue. The combinations and their dosages are modified according to the presence of risk factors. Imatinib can be added to the drug regimen in patients with Ph chromosome-positive ALL.

CNS prophylaxis: An important site of leukemic infiltration is the meninges; prophylaxis and treatment may include high-dose intrathecal methotrexate, cytosine arabinoside, and corticosteroids. Cranial nerve or whole-brain irradiation may be necessary and is often used for patients at high risk of CNS disease (eg, high WBC count, high serum LDH, B-cell phenotype) but has been used less often in recent years.

Consolidation therapy: The goal of consolidation is to prevent leukemic regrowth. Consolidation therapy usually lasts a few months and combines drugs that have different mechanisms of action than drugs used in induction regimens. Allogeneic stem cell transplantation is recommended as consolidation of Ph chromosome-positive ALL or in 2nd or later relapses or remissions.

Maintenance therapy: Most regimens include maintenance therapy with methotrexate and mercaptopurine. Therapy duration is usually 2 1/2 to 3 yr but may be shorter with regimens that are more intensive in earlier phases and for B-cell (L3) cases. For patients in continuous complete remission for 2 1/2 yr, the risk of relapse after therapy cessation is about 20%, usually within 1 yr. Thus, when therapy can be stopped, most patients are cured.

Relapse: Leukemic cells may reappear in the bone marrow, the CNS, or the testes. Bone marrow relapse is particularly ominous. Although a new round of chemotherapy may induce a 2nd remission in 80 to 90% of children (30 to 40% of adults), subsequent remissions tend to be brief. Only a few patients with late bone marrow relapses achieve long disease-free 2nd remissions or cure.

If an HLA-matched sibling is available, stem cell transplantation offers the greatest hope of long-term remission or cure (see p. 1132). Cells from other relatives or matched, unrelated donors are sometimes used. Transplantation is rarely used for patients > 65 yr because it is much less likely to be successful and because adverse effects are much more likely to be fatal.

When relapse involves the CNS, treatment includes intrathecal methotrexate (with or without cytarabine or corticosteroids) twice weekly until all signs disappear. Most regimens include systemic reinduction chemotherapy because of the likelihood of systemic spread of blast cells. The role of continued intrathecal drug use or CNS irradiation is unclear.

Testicular relapse may be evidenced clinically by painless firm swelling of the testis or may be identified on biopsy. If unilateral testicular involvement is clinically evident, the apparently uninvolved testis should undergo biopsy. Treatment is by irradiation of the involved testis and administration of systemic reinduction therapy as for isolated CNS relapse.

Acute Myelocytic Leukemia

(Acute Myelogenous Leukemia; Acute Myeloid Leukemia)

In AML, malignant transformation and uncontrolled proliferation of an abnormally differentiated, long-lived myeloid progenitor cell results in high circulating numbers of immature blood forms and replacement of normal marrow by malignant cells. Symptoms include fatigue, pallor, easy bruising and bleeding, fever, and infection; symptoms of leukemic infiltration are present in only about 5% of patients (often as skin manifestations). Examination of peripheral smear and bone marrow is diagnostic. Treatment includes induction chemotherapy to achieve remission and postremission chemotherapy (with or without stem cell transplantation) to avoid relapse.

The incidence of AML increases with age; it is the more common acute leukemia in adults, with a median age of onset of 50 yr. AML may occur as a secondary cancer after chemotherapy or irradiation for a different type of cancer.

AML has a number of subtypes that are distinguished from each other by morphology, immunophenotype, and cytochemistry. Five classes are described, based on predominant cell type, including myeloid, myeloid-monocytic, monocytic, erythroid, and megakaryocytic.

Acute promyelocytic leukemia (APL) is a particularly important subtype, representing 10 to 15% of all cases of AML, striking a younger age group (median age 31 yr) and particular ethnicity (Hispanics), in which the patient commonly presents with a coagulation disorder.

Prognosis

Remission induction rates range from 50 to 85%. Long-term disease-free survival reportedly occurs in 20 to 40% of patients and increases to 40 to 50% in younger patients treated with stem cell transplantation.

Prognostic factors help determine treatment protocol and intensity; patients with strongly negative prognostic features are usually given more intense forms of therapy, because the potential benefits are thought to justify the increased treatment toxicity. The most important prognostic factor is the leukemia cell karyotype. The specific chromosomal rearrangements of the different forms of AML can affect the outcome. Three levels of outcome have been identified: favorable, intermediate, and poor. Patients who have the cytogenetics t(8;21), t(15;17), and inv(16) typically have a favorable response to therapy, remission duration, and survival. Patients with a normal karyotype have an intermediate prognosis, and patients with a poor prognosis are those with a deletion of chromosome 5 or 7, trisomy 8, or a karyotype with > 3 abnormalities. Other negative factors include increasing age, a preceding myelodysplastic phase, secondary leukemia, high WBC count, and absence of Auer rods. The FAB or WHO classification alone does not predict response.

Treatment

• Chemotherapy (induction and consolidation)

• Sometimes stem cell transplantation

Induction therapy: Initial therapy attempts to induce remission and differs most from ALL in that AML responds to fewer drugs. The basic induction regimen includes cytarabine by continuous IV infusion or high doses for 5 to 7 days; daunorubicin or idarubicin is given IV for 3 days during this time. Some regimens include 6-thioguanine, etoposide, vincristine, and prednisone, but their contribution is unclear. Treatment usually results in significant myelosuppression, with infection or bleeding; there is significant latency before marrow recovery. During this time, meticulous preventive and supportive care is vital (see p. 1007).

In APL and some other cases of AML, disseminated intravascular coagulation (DIC) may be present on diagnosis and may worsen as leukemic cell lysis releases procoagulant. In APL with the translocation t(15;17), all-*trans*-retinoic acid corrects the DIC in 2 to 5 days; combined with daunorubicin or idarubicin,

this regimen can induce remission in 80 to 90% of patients and bring about long-term survival in 65 to 70%. Arsenic trioxide is also very active in APL.

Consolidation therapy: After remission, many regimens involve a phase of intensification with the same drugs used for induction or with other drugs. High-dose cytarabine regimens may lengthen remission duration, particularly when given as consolidation in patients < 60 yr. CNS prophylaxis usually is not given, because with better systemic disease control, CNS leukemia is a less frequent complication. In AML patients who have had consolidation, maintenance therapy has no demonstrated role.

Relapse: Patients who have not responded to treatment and younger patients who are in remission but who are at high risk of relapse (generally identified by certain chromosomal abnormalities) may be given high-dose chemotherapy and stem cell transplantation. Extramedullary sites are infrequently involved in isolated relapse. When relapse occurs, additional chemotherapy for patients unable to undergo stem cell transplantation is less effective and often poorly tolerated. Another course of chemotherapy is most effective in younger patients and in patients whose initial remission lasted > 1 yr. Gemtuzumab ozogamicin, a recombinant monoclonal antibody combined with a cytotoxic drug, is effective in some patients after relapse has occurred, but long-term benefits have not been determined.

Chronic Leukemia

Chronic leukemia usually manifests as abnormal leukocytosis with or without cytopenia in an otherwise asymptomatic person. Findings and management differ significantly between chronic lymphocytic leukemia (CLL) and chronic myelocytic leukemia (CML).

Chronic Lymphocytic Leukemia

(Chronic Lymphatic Leukemia)

The most common type of leukemia in the Western world, CLL involves mature-appearing defective neoplastic lymphocytes (almost always B cells) with an abnormally long life span. The peripheral blood, bone marrow, spleen, and lymph nodes undergo leukemic infiltration. Symptoms may be absent or may include lymphadenopathy, splenomegaly, hepatomegaly, and nonspecific symptoms attributable to anemia (fatigue, malaise). Diagnosis is by examination of peripheral smear and bone marrow aspirate. Treatment, delayed until symptoms develop, is aimed at lengthening life and decreasing symptoms and may involve chlorambucil or fludarabine, prednisone, and cyclophosphamide or doxorubicin or both. Monoclonal antibodies, such as alemtuzumab and rituximab, are increasingly being used. Palliative radiation therapy is reserved for patients whose lymphadenopathy or splenomegaly interferes with other organs.

Incidence of CLL increases with age; 75% of cases are diagnosed in patients > 60 yr. CLL is twice as common in men. Although the cause is unknown, some cases appear to have a hereditary component. CLL is rare in Japan and China and does not seem to increase among Japanese expatriates in the US, suggesting a genetic factor. CLL is more common among Jews of Eastern European descent.

Pathophysiology

In about 98% of cases, CD5+ B cells undergo malignant transformation, with lymphocytes initially accumulating in the bone marrow and then spreading to lymph nodes and other lymphoid tissues, eventually inducing splenomegaly and hepatomegaly. As CLL progresses, abnormal hematopoiesis results in anemia, neutropenia, thrombocytopenia, and decreased immunoglobulin production. Many patients develop hypogammaglobulinemia and impaired antibody response, perhaps related to increased T-suppressor cell activity. Patients have increased susceptibility to autoimmune disease characterized by immunohemolytic anemias (usually Coombs' test-positive) or thrombocytopenia and a modest increase in risk of developing other cancers.

In 2 to 3% of cases, the clonal expansion is T cell in type, and even this group has a subtype (eg, large granular lymphocytes with cytopenias).

In addition, other chronic leukemic patterns have been categorized under CLL:

• Prolymphocytic leukemia

• Leukemic phase of cutaneous T-cell lymphoma (ie, Sezary syndrome)

• Hairy cell leukemia

• Lymphoma leukemia (ie, leukemic changes that occur in advanced stages of malignant lymphoma)

Differentiation of these subtypes from typical CLL is usually straightforward.

Symptoms and Signs

Onset is usually insidious; CLL is often diagnosed incidentally during routine blood tests or through evaluation of asymptomatic lymphadenopathy. Symptomatic patients usually have nonspecific complaints of fatigue, anorexia, weight loss, dyspnea on exertion, or a sense of abdominal fullness (secondary to an enlarged spleen). Initial findings include generalized lymphadenopathy and minimal-to-moderate hepatomegaly and splenomegaly. With progressive disease, there may be pallor due to anemia. Skin infiltration, either maculopapular or diffuse, may be a feature of T-cell CLL. Hypogammaglobulinemia and granulocytopenia in late CLL may predispose to bacterial, viral, and fungal infection, especially pneumonia. Herpes zoster is common and usually dermatomic.

Diagnosis

• CBC and peripheral smear

• Bone marrow examination

• Immunophenotyping

CLL is confirmed by examining the peripheral smear and bone marrow; the hallmark is sustained, absolute peripheral lymphocytosis (> 5000/μL) and increased lymphocytes (> 30%) in the bone marrow. Differential diagnosis is simplified by immunophenotyping. Other findings at diagnosis may include hypogammaglobulinemia (< 15% of cases) and, rarely, elevated LDH. Only 10% of patients present with moderate anemia (sometimes immunohemolytic), thrombocytopenia, or both. A monoclonal serum immunoglobulin spike of the same type may be found on the leukemic cell surface in 2 to 4% of cases.

Clinical staging is useful for prognosis and treatment. Two common approaches are Rai and Binet staging, primarily based on hematologic changes and extent of disease (see Table 117-3).

Prognosis

The median survival of patients with B-cell CLL or its complications is about 7 to 10 yr. Patients in Rai stage 0 to II at diagnosis may survive for 5 to 20 yr without treatment. Patients in Rai stage III or IV are more likely to die within 3 to 4 yr of diagnosis. Progression to bone marrow failure is usually associated with short survival. Patients with CLL are more likely to develop a secondary cancer, especially skin cancer.

Treatment

• Symptom amelioration

• Supportive care

Although CLL is progressive, some patients may be asymptomatic for years; therapy is not indicated until progression or symptoms occur. Cure usually is not possible, so treatment attempts to ameliorate

symptoms and prolong life. Supportive care includes transfusion of packed RBCs or erythropoietin injections for anemia; platelet transfusions for bleeding associated with thrombocytopenia; and antimicrobials for bacterial, fungal, or viral infections. Because neutropenia and agammaglobulinemia limit bacterial killing, antibiotic therapy should be bactericidal. Therapeutic infusions of γ-globulin should be considered in patients with hypogammaglobulinemia and repeated or refractory infections or, for prophylaxis, when ≥ 2 severe infections occur within 6 mo.

[**Table 117-3.** Clinical Staging of Chronic Lymphocytic Leukemia]

Specific therapy includes

• Chemotherapy

• Corticosteroids

• Monoclonal antibody therapy

• Radiation therapy

These modalities may alleviate symptoms but have not been proven to prolong survival. *Overtreatment is more dangerous than under-treatment*.

Chemotherapy: Chemotherapy may be instituted in response to the advent of symptomatic disease, including constitutional symptoms (fever, night sweats, extreme fatigue, weight loss); significant hepatomegaly, splenomegaly, or lymphadenopathy; lymphocytosis > 100,000/μL; and infections accompanied by anemia, neutropenia, or thrombocytopenia. Alkylating drugs, especially chlorambucil, alone or with corticosteroids, have long been the usual therapy for B-cell CLL. However, fludarabine is more effective. Combination chemotherapy with fludarabine, cyclophosphamide, and rituximab more often induces complete remissions. It also lengthens remission duration and prolongs survival. Interferon alfa, deoxycoformycin, and 2-chlorodeoxyadenosine are highly effective for hairy cell leukemia. Patients with prolymphocytic leukemia and lymphoma leukemia usually require multidrug chemotherapy and often respond only partially.

Corticosteroids: Immunohemolytic anemia and thrombocytopenia are indications for corticosteroids. Prednisone 1 mg/kg po once/day may occasionally result in striking, rapid improvement in patients with advanced CLL, although response is often brief. The metabolic complications and increasing rate and severity of infections warrant caution in its prolonged use. Prednisone used with fludarabine increases the risk of *Pneumocystis jirovecii* and *Listeria* infections.

Monoclonal antibody therapy: Rituximab is the first monoclonal antibody used in the successful treatment of lymphoid cancers. The partial response rate with conventional doses in CLL is 10 to 15%. In previously untreated patients, the response rate is 75%, with 20% of patients achieving complete remission. Alemtuzumab has a 33% response rate in previously treated patients refractory to fludarabine and a 75 to 80% response rate in previously untreated patients. More problems with immunosuppression occur with alemtuzumab than with rituximab. Rituximab has been combined with fludarabine and with fludarabine and cyclophosphamide; these combinations have markedly improved the complete remission rate in both previously treated and untreated patients. Alemtuzumab is now being combined with rituximab and with chemotherapy to treat minimal residual disease and has effectively cleared bone marrow infiltration. Reactivation of cytomegalovirus and other opportunistic infections has occurred with alemtuzumab.

Radiation therapy: Local irradiation may be given to areas of lymphadenopathy or liver and spleen involvement for transient symptomatic palliation. Total body irradiation in small doses is occasionally successful.

Chronic Myelocytic Leukemia

(Chronic Granulocytic Leukemia; Chronic Myelogenous Leukemia; Chronic Myeloid Leukemia)

CML occurs when a pluripotent stem cell undergoes malignant transformation and clonal myeloproliferation, leading to a striking overproduction of immature granulocytes. Initially asymptomatic, CML progression is insidious, with a nonspecific "benign" stage (malaise, anorexia, weight loss) eventually giving way to accelerated or blast phases with more ominous signs, such as splenomegaly, pallor, easy bruising and bleeding, fever, lymphadenopathy, and skin changes. Peripheral smear, bone marrow aspirate, and demonstration of Philadelphia chromosome are diagnostic. Treatment is with imatinib, which significantly improves response and probably prolongs survival. The curative potential of imatinib is undefined. Myelosuppressive drugs (eg, hydroxyurea), stem cell transplantation, and interferon alfa are also used.

CML accounts for about 15% of all adult leukemias. CML can strike at any age, although it is uncommon before age 10, and the median age at diagnosis is 45 to 55. CML may occur in either sex.

Pathophysiology

Most cases of CML appear to be induced by a translocation known as the Philadelphia (Ph) chromosome, which is demonstrable in 95% of patients. It is a reciprocal translocation t(9;22) in which a piece of chromosome 9 containing the oncogene *c-abl* is translocated to chromosome 22 and fused to the gene *BCR*. The fusion gene *BCR-ABL* is important in the pathogenesis and expression of CML and results in the production of a specific tyrosine kinase. CML ensues when an abnormal pluripotent hematopoietic progenitor cell initiates excessive production of granulocytes, primarily in the bone marrow but also in extramedullary sites (eg, spleen, liver). Although granulocyte production predominates, the neoplastic clone includes RBC, megakaryocyte, monocyte, and even some T and B cells. Normal stem cells are retained and can emerge after drug suppression of the CML clone.

CML has 3 phases:

- **Chronic phase:** An initial indolent period that may last months to years
- **Accelerated myeloproliferative phase:** Treatment failure, worsening anemia, and progressive thrombocytopenia
- **Terminal phase:** Blast crisis; blast cell tumors possibly developing in extramedullary sites (eg, bone, CNS, lymph nodes, skin)

The terminal phase leads to fulminant complications resembling those of acute leukemia, including sepsis and bleeding. Some patients progress directly from the chronic to the blast phase.

Symptoms and Signs

Patients are often asymptomatic early on, with insidious onset of nonspecific symptoms (eg, fatigue, weakness, anorexia, weight loss, fever, night sweats, a sense of abdominal fullness), which may prompt evaluation. Initially, pallor, bleeding, easy bruising, and lymphadenopathy are unusual, but moderate or occasionally extreme splenomegaly is common (60 to 70% of cases). With disease progression, splenomegaly may increase, and pallor and bleeding occur. Fever, marked lymphadenopathy, and maculopapular skin involvement are ominous developments.

Diagnosis

- CBC and peripheral smear
- Bone marrow examination
- Cytogenetic studies (Ph chromosome)

CML is most frequently diagnosed by a CBC obtained incidentally or during evaluation of splenomegaly.

Granulocyte count is elevated, usually < 50,000/μL in asymptomatic patients and 200,000/μL to 1,000,000/μL in symptomatic patients, and platelet count is normal or moderately increased. Hb level is usually > 10 g/dL.

Peripheral smear may help differentiate CML from leukocytosis of other etiology. In CML, peripheral smear shows predominantly immature granulocytes and absolute eosinophilia and basophilia, although in patients with WBC counts < 50,000/μL, immature granulocytes may be uncommon. Leukocytosis in patients with myelofibrosis is usually associated with nucleated RBCs, teardrop-shaped RBCs, anemia, and thrombocytopenia. Myeloid leukemoid reactions resulting from cancer or infection are not often associated with absolute eosinophilia and basophilia.

The leukocyte alkaline phosphatase score is usually low in CML and increased in leukemoid reactions. Bone marrow examination should be done to evaluate the karyotype as well as cellularity (usually increased) and extent of myelofibrosis.

Diagnosis is confirmed by presence of the Ph chromosome on cytogenetic or molecular studies, although it is absent in 5% of patients.

During the accelerated phase of disease, anemia and thrombocytopenia usually develop. Basophils may increase, and granulocyte maturation may be defective. The proportion of immature cells and the leukocyte alkaline phosphatase score may increase. In the bone marrow, myelofibrosis may develop and sideroblasts may be seen on microscopy. Evolution of the neoplastic clone may be associated with development of new abnormal karyotypes, often an extra chromosome 8 or isochromosome 17.

Further evolution may lead to a blast crisis with myeloblasts (60% of patients), lymphoblasts (30%), and megakaryocytoblasts (10%). In 80% of these patients, additional chromosomal abnormalities occur frequently.

Prognosis

With imatinib, survival is > 90% at 5 yr after diagnosis. Before imatinib was used, with treatment 5 to 10% of patients died within 2 yr of diagnosis; 10 to 15% died each year thereafter. Median survival was 4 to 7 yr. Most (90%) deaths follow a blast crisis or an accelerated phase of the disease. Median survival after blast crisis is about 3 to 6 mo but can be up to 12 mo with remission.

Ph chromosome-negative CML and chronic myelomonocytic leukemia have a worse prognosis than Ph chromosome-positive CML. Their clinical behaviors resemble a myelodysplastic syndrome (see p. 1014).

Treatment

• A tyrosine kinase inhibitor, sometimes with chemotherapy

• Sometimes stem cell transplantation

Except when stem cell transplantation is successful, treatment is not curative; however, survival can be prolonged by treatment with imatinib.

Imatinib and several newer drugs inhibit the specific tyrosine kinase that results from the *BCR-ABL* gene product. It is dramatically effective in achieving complete clinical and cytogenetic remissions of Ph chromosome-positive CML and is clearly superior to other regimens (eg, interferon with or without cytosine arabinoside). Imatinib also is superior to other treatments in the accelerated and blast phases. In blast crisis, combinations of chemotherapy with imatinib have a higher response rate than does therapy with either approach alone. Treatment tolerance is excellent. The high level of durable complete remissions associated with imatinib therapy has led to the prospect of cure of the disease.

Older chemotherapy regimens are reserved for *BCR-ABL*-negative patients, patients who relapse after receiving imatinib, and patients in blast crisis. The main agents are busulfan, hydroxyurea, and interferon. Hydroxyurea is easiest to manage and has the fewest adverse effects. The starting dosage is generally

500 to 1000 mg po bid. Blood counts should be done every 1 to 2 wk and the dosage adjusted accordingly. Busulfan often causes unexpected general myelosuppression, and interferon causes a flu-like syndrome that often is unacceptable to patients. The main benefit of these therapies is reduction in distressing splenomegaly and adenopathy and control of the tumor burden to reduce the incidence of tumor lysis and gout. None of these therapies prolongs median survival > 1 yr compared with untreated patients; thus, reduction in symptoms is the major goal, and therapy is not continued when patients have significant toxic symptoms.

Allogeneic stem cell transplantation can be useful for patients refractory to frontline therapy.

Although splenic radiation is rarely used, it may be helpful in refractory cases of CML or in patients with terminal disease and marked splenomegaly. Total dosage usually ranges from 6 to 10 Gy delivered in fractions of 0.25 to 2 Gy/day. Treatment should begin with very low doses and careful evaluation of the WBC count. Response is usually disappointing.

Splenectomy may alleviate abdominal discomfort, lessen thrombocytopenia, and relieve transfusion requirements when splenomegaly cannot be controlled with chemotherapy or irradiation. Splenectomy does not play a significant role during the chronic phase of CML.

Myelodysplastic Syndrome

Myelodysplastic syndrome (MDS) involves a group of disorders typified by peripheral cytopenia, dysplastic hematopoietic progenitors, a hypercellular bone marrow, and a high risk of conversion to acute myelocytic leukemia (AML). Symptoms are referable to the specific cell line most affected and may include fatigue, weakness, pallor (secondary to anemia), increased infections and fever (secondary to neutropenia), and increased bleeding and bruising (secondary to thrombocytopenia). Diagnosis is by blood count, peripheral smear, and bone marrow aspiration. Treatment with 5-azacytidine may help; if AML supervenes, it is treated per the usual protocols.

Pathophysiology

MDS is a group of disorders, often termed preleukemia, refractory anemias, Philadelphia chromosome-negative chronic myelocytic leukemia, chronic myelomonocytic leukemia, or agnogenic myeloid metaplasia, resulting from a somatic mutation of hematopoietic precursors. Etiology is often unknown, but risk is increased with exposure to benzene, radiation, and chemotherapeutic agents (particularly long or intense regimens and those involving alkylating agents and epipodophyllotoxins).

MDS is characterized by clonal proliferation of hematopoietic cells, including erythroid, myeloid, and megakaryocytic forms. The bone marrow is normal or hypercellular, and ineffective hematopoiesis can cause anemia (most common), neutropenia, thrombocytopenia, or a combination. The disordered cell production is also associated with morphologic cellular abnormalities in bone marrow and blood. Extramedullary hematopoiesis may occur, leading to hepatomegaly and splenomegaly. Myelofibrosis is occasionally present at diagnosis or may develop during the course of MDS. Classification is by blood and bone marrow findings (see
Table 117-4). The MDS clone is unstable and tends to progress to AML.

Symptoms and Signs

Symptoms tend to reflect the most affected cell line and may include pallor, weakness, and fatigue (anemia); fever and infections (neutropenia); and increased bruising, petechiae, epistaxis, and mucosal bleeding (thrombocytopenia). Splenomegaly and hepatomegaly are common. Symptoms may also be referable to other underlying disorders; eg, in elderly patients with preexisting cardiovascular disorders, anemia from MDS may exacerbate anginal pain.

Diagnosis

• CBC

• Peripheral smear

• Bone marrow examination

MDS is suspected in patients (especially the elderly) with refractory anemia, leukopenia, or thrombocytopenia. Cytopenias secondary to congenital disorders, vitamin deficiencies, or drug adverse effects must be ruled out. Diagnosis

[Table 117-4. Myelodysplastic Syndrome Bone Marrow Findings and Survival]

is by examining peripheral blood and bone marrow and identifying morphologic abnormalities in 10 to 20% of cells of a particular lineage.

Anemia is the most common feature, associated usually with macrocytosis and anisocytosis. With automatic cell counters, these changes are indicated by an increased MCV and RBC distribution width. Some degree of thrombocytopenia is usual; on peripheral smear, platelets vary in size, and some appear hypogranular. The WBC count may be normal, increased, or decreased. Neutrophil cytoplasmic granularity is abnormal, with anisocytosis and variable numbers of granules. Eosinophils also may have abnormal granularity. Pseudo Pelger-Huet cells (hyposegmented neutrophils) may be seen. Monocytosis is characteristic of the chronic myelomonocytic leukemia subgroup, and immature myeloid cells may occur in the less well differentiated subgroups. The cytogenetic pattern is usually abnormal, with one or more clonal cytogenetic abnormalities often involving chromosomes 5 or 7.

Prognosis

Prognosis depends greatly on classification and on any associated disorder. Patients with refractory anemia or refractory anemia with sideroblasts are less likely to progress to the more aggressive forms and may die of unrelated causes.

Treatment

• Symptom amelioration

• Supportive care

• Possibly stem cell transplantation

Azacitidine relieves symptoms, decreases the rate of transformation to leukemia and the need for transfusions, and probably improves survival. Other therapy is supportive, including RBC transfusions as indicated, platelet transfusions for bleeding, and antibiotic therapy for bacterial infection. Deoxyazacitidine, a hypomethylating agent, is sometimes effective, even in patients who do not respond to azacitidine. In some patients, erythropoietin to support RBC needs, granulocyte colony-stimulating factor to manage severe symptomatic granulocytopenia, and, when available, thrombopoietin for severe thrombocytopenia can serve as important hematopoietic support but have not increased survival. Allogeneic stem cell transplantation is useful, and nonablative allogeneic bone marrow transplantations are now being studied for patients > 50 yr. Response of MDS to chemotherapy used for AML is similar to that of AML, after age and karyotype are considered.

Chapter 118. Lymphomas

Introduction

Lymphomas are a heterogeneous group of tumors arising in the reticuloendothelial and lymphatic systems. The major types are Hodgkin lymphoma and non-Hodgkin lymphoma (NHL—see Table 118-1).

Lymphomas were once thought to be absolutely distinct from leukemias. However, better understanding of cell markers and tools with which to evaluate those markers now show that the differentiation between these 2 cancers is often vague. The notion that lymphoma is relatively restricted to the lymphatic system and leukemias to the bone marrow, at least in early stages, is also not always true.

Hodgkin Lymphoma

(Hodgkin's Disease)

Hodgkin lymphoma is a localized or disseminated malignant proliferation of cells of the lymphoreticular system, primarily involving lymph node tissue, spleen, liver, and bone marrow. Symptoms include painless lymphadenopathy, sometimes with fever, night sweats, unintentional weight loss, pruritus, splenomegaly, and hepatomegaly. Diagnosis is based on lymph node biopsy. Treatment is curative in about 75% of cases and consists of chemotherapy with or without radiation therapy.

In the US, about 8000 new cases of Hodgkin lymphoma are diagnosed annually. The male:female ratio is 1.4:1. Hodgkin lymphoma is rare before age 10 and is most common between ages 15 and 40; a 2nd peak occurs in people > 50 to 60.

Pathophysiology

Hodgkin lymphoma results from the clonal transformation of cells of B-cell origin, giving rise to pathognomic binucleated Reed-Sternberg cells. The cause is unknown, but genetic susceptibility and environmental associations (eg, occupation, such as woodworking; history of treatment with phenytoin, radiation therapy, or chemotherapy; infection with Epstein-Barr virus, *Mycobacterium tuberculosis*, herpesvirus type 6, HIV) play a role. Risk is slightly increased in people with certain types of immunosuppression (eg, posttransplant patients taking immunosuppressants); in people with congenital immunodeficiency states (eg, ataxia-telangiectasia, Klinefelter's syndrome, Chediak-Higashi syndrome, Wiskott-Aldrich syndrome); and in people with certain autoimmune disorders (RA, celiac sprue, Sjogren's syndrome, SLE).

[**Table 118-1.** Comparison of Hodgkin Lymphoma and Non-Hodgkin Lymphoma]

Most patients also develop a slowly progressive defect in cell-mediated immunity (T-cell function) that, in advanced disease, contributes to common bacterial and unusual fungal, viral, and protozoal infections. Humoral immunity (antibody production) is depressed in advanced disease. Death often results from sepsis.

Symptoms and Signs

Most patients present with painless cervical adenopathy. Although the mechanism is unclear, pain may occur in diseased areas immediately after drinking alcoholic beverages, thereby providing an early indication of the diagnosis.

Other manifestations develop as the disease spreads through the reticuloendothelial system, generally to contiguous sites. Intense pruritus may occur early. Constitutional symptoms include fever, night sweats, and unintentional weight loss (> 10% of body weight in previous 6 mo), which may signify involvement of internal lymph nodes (mediastinal or retroperitoneal), viscera (liver), or bone marrow. Splenomegaly is often present; hepatomegaly may be present. Pel-Ebstein fever (a few days of high fever regularly

alternating with a few days to several weeks of normal or below-normal temperature) occasionally occurs. Cachexia is common as disease advances.

Bone involvement is often asymptomatic but may produce vertebral osteoblastic lesions (ivory vertebrae) and, rarely, pain with osteolytic lesions and compression fracture. Intracranial, gastric, and cutaneous lesions are rare and when present suggest HIV-associated Hodgkin lymphoma.

Local compression by tumor masses often causes symptoms, including

• Jaundice secondary to intrahepatic or extrahepatic bile duct obstruction

• Leg edema secondary to lymphatic obstruction in the pelvis or groin

• Severe dyspnea and wheezing secondary to tracheobronchial compression

• Lung cavitation or abscess secondary to infiltration of lung parenchyma, which may simulate lobar consolidation or bronchopneumonia

Epidural invasion that compresses the spinal cord may result in paraplegia. Horner's syndrome and laryngeal paralysis may result when enlarged lymph nodes compress the cervical sympathetic and recurrent laryngeal nerves. Neuralgic pain follows nerve root compression.

Diagnosis

• Chest x-ray

• CT of chest, abdomen, and pelvis

• CBC, ESR, alkaline phosphatase, LDH, liver function tests, albumin, Ca, BUN, and creatinine

• Lymph node biopsy

• Bone marrow biopsy

• Possibly PET for staging, bone scanning if bone pain is present, or MRI if neurologic symptoms are present

Hodgkin lymphoma is usually suspected in patients with painless lymphadenopathy or mediastinal adenopathy detected on routine chest x-ray. Similar lymphadenopathy can result from infectious mononucleosis, toxoplasmosis, cytomegalovirus infection, non-Hodgkin lymphoma, or leukemia. Similar chest x-ray findings can result from lung cancer, sarcoidosis, or TB (for evaluation of a mediastinal mass, see p. 1994).

A chest x-ray is obtained if not already done. X-ray is usually followed by lymph node biopsy if findings are confirmed on CT or PET scan of the chest. If only mediastinal nodes are enlarged, mediastinoscopy or Chamberlain procedure (a limited left anterior thoracostomy allowing biopsy of mediastinal lymph nodes inaccessible by cervical mediastinoscopy) may be indicated. CT-guided biopsy may also be considered, but results of fine-needle aspiration are often inaccurate, so lymph node biopsy is preferred. CBC, ESR, alkaline phosphatase, and renal and liver function tests are generally done. Other tests are done depending on findings (eg, MRI for symptoms of cord compression, bone scan for evaluation of bone pain).

Biopsy reveals Reed-Sternberg cells (large binucleated cells) in a characteristically heterogeneous cellular infiltrate consisting of histiocytes, lymphocytes, monocytes, plasma cells, and eosinophils. Classic Hodgkin lymphoma has 4 histopathologic subtypes (see Table 118-2); there is also a lymphocyte-predominant type. Certain antigens on Reed-Sternberg cells may help differentiate Hodgkin lymphoma from non-Hodgkin lymphoma, and classic Hodgkin lymphoma from

the lymphocyte-predominant type.

Other test results may be abnormal but are nondiagnostic. CBC may show slight polymorphonuclear leukocytosis. Lymphocytopenia may occur early and become pronounced with advanced disease. Eosinophilia is present in about 20% of patients, and thrombocytosis may be present. Anemia, often microcytic, usually develops with advanced disease. In advanced anemia, defective iron reutilization is characterized by low serum iron, low iron-binding capacity, and increased bone marrow iron. Pancytopenia is occasionally caused by bone marrow invasion, usually by the lymphocyte-depleted type. Hypersplenism (see p. 985) may appear in patients with marked splenomegaly. Elevated serum alkaline phosphatase levels may be present, but elevations do not always indicate bone marrow or liver involvement. Increases in leukocyte alkaline phosphatase, serum haptoglobin, ESR, and other acute-phase reactants usually reflect active disease.

Staging: After diagnosis, stage is determined to guide therapy. The commonly used Ann Arbor staging system (see Table 118-3) incorporates symptoms; physical examination findings; results of imaging tests, including chest x-ray, CT of the chest, abdomen, and pelvis; and unilateral bone marrow biopsy. Laparotomy is not required for staging. Other

[**Table 118-2.** Histopathologic Subtypes of Hodgkin Lymphoma (WHO Classification)]

staging tests may include PET scan and cardiac and pulmonary function tests in anticipation of therapy. The Cotswold modifications of the Ann Arbor staging system incorporate the prognostic implications of tumor bulkiness and numerous disease sites.

Designation of the letter A to any stage means that no systemic symptoms are being experienced. Designation of the letter B means that at least one systemic symptom is experienced. The presence of symptoms correlates with response to treatment.

Prognosis

In classic Hodgkin lymphoma, disease-free survival 5 yr after therapy is considered a cure. Relapse is very rare after 5 yr. Chemotherapy with or without radiation therapy achieves cure in 70 to 80% of patients. Increased potential for relapse depends on many factors, including male sex, age > 45 yr, involvement of multiple extranodal sites, and presence of constitutional symptoms at diagnosis. Patients who do not achieve complete remission or who relapse within 12 mo have a poor prognosis.

Treatment

- Chemotherapy
- Radiation therapy
- Surgery
- Sometimes hematopoietic stem cell transplantation

The choice of treatment modality is complex and depends on the precise stage of disease. Before treatment, men should be offered sperm banking, and women should discuss fertility options with their oncologists.

Stage IA, IIA, IB, or IIB disease is generally treated with an abbreviated chemotherapy regimen of doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (ABVD) plus radiation therapy or with longer-course chemotherapy alone. Such treatment cures about 80% of patients. In patients with bulky mediastinal disease, chemotherapy may be of longer duration or of a different type, and radiation therapy is used routinely.

Stage IIIA disease is usually treated with ABVD combination chemotherapy. Involved field irradiation is

also sometimes added. Cure rates of 75 to 80% have been achieved.

[**Table 118-3.** Cotswold Modification of Ann Arbor Staging of Hodgkin Lymphoma and Non-Hodgkin Lymphoma]

Stage IIIB disease requires ABVD combination chemotherapy typically alone but sometimes with involved field irradiation. Survival rates range from 70 to 80%.

For stage IVA and IVB disease, ABVD combination chemotherapy is the standard regimen, producing complete remission in 70 to 80% of patients; > 50% remain disease-free at 5 yr. Other effective drugs include nitrosoureas, ifosfamide, cisplatin or carboplatin, and etoposide. A promising new drug combination, Stanford V, is a 12-wk regimen that incorporates involved field irradiation for consolidation.

Autologous transplantation using peripheral stem cell products should be considered for all physiologically eligible patients with relapsed or refractory Hodgkin lymphoma who respond to salvage chemotherapy.

Complications of treatment: Chemotherapy with mechlorethamine, vincristine (Oncovin), procarbazine, and prednisone (MOPP) and MOPP-like regimens increases the risk of leukemia, which generally develops after > 3 yr. Both chemotherapy and radiation therapy increase the risk of malignant solid tumors (eg, breast, GI, lung, soft tissue). Mediastinal radiation increases the risk of coronary atherosclerosis. Breast cancer risk is increased in women beginning about 7 yr after they have received radiation treatment to adjacent nodal regions.

Posttreatment surveillance: Routine testing is done to identify recurrence. For a schedule of posttreatment surveillance, see Table 118-4.

[**Table 118-4.** Hodgkin Lymphoma Posttreatment Surveillance]

Non-Hodgkin Lymphomas

Non-Hodgkin lymphomas (NHL) are a heterogeneous group of disorders involving malignant monoclonal proliferation of lymphoid cells in lymphoreticular sites, including lymph nodes, bone marrow, the spleen, the liver, and the GI tract. Presenting symptoms usually include peripheral lymphadenopathy. However, some patients present without lymphadenopathy but with abnormal lymphocytes in circulation. Compared with Hodgkin lymphoma, there is a greater likelihood of disseminated disease at the time of diagnosis. Diagnosis is usually based on lymph node or bone marrow biopsy or both. Treatment involves radiation therapy, chemotherapy, or both. Stem cell transplantation is usually reserved for salvage therapy after incomplete remission or relapse.

NHL is more common than Hodgkin lymphoma. It is the 6th most common cancer in the US; about 65,000 new cases are diagnosed annually in all age groups. However, NHL is not one disease but rather a category of lymphocyte cancers. Incidence increases with age (median age, 50 yr).

Etiology

The cause of NHL is unknown, although, as with the leukemias, substantial evidence suggests a viral cause (eg, human T-cell leukemia-lymphoma virus, Epstein-Barr virus, hepatitis C virus, HIV). Risk factors for NHL include immunodeficiency (secondary to posttransplant immunosuppression, AIDS, primary immune disorders, sicca syndrome, RA), *Helicobacter pylori* infection, certain chemical exposures, and previous treatment for Hodgkin lymphoma. NHL is the 2nd most common cancer in HIV-infected patients (see p. 1457), and some AIDS patients present with lymphoma. *C-myc* gene rearrangements are characteristic of some AIDS-associated lymphomas.

Pathophysiology

Most (80 to 85%) NHLs arise from B cells; the remainder arise from T cells or natural killer cells. Either precursor or mature cells may be involved. Overlap exists between leukemia and NHL because both involve proliferation of lymphocytes or their precursors. A leukemia-like picture with peripheral lymphocytosis and bone marrow involvement may be present in up to 50% of children and in about 20% of adults with some types of NHL. Differentiation can be difficult, but generally patients with more extensive nodal involvement (especially mediastinal), fewer circulating abnormal cells, and fewer blast forms in the marrow (< 25%) are considered to have lymphoma. A prominent leukemic phase is less common in aggressive lymphomas, except Burkitt's and lymphoblastic lymphomas.

Hypogammaglobulinemia caused by a progressive decrease in immunoglobulin production occurs in 15% of patients and may predispose to serious bacterial infection.

Classification

Pathologic classification of NHLs continues to evolve, reflecting new insights into the cells of origin and the biologic bases of these heterogeneous diseases. The WHO classification (see Table 118-5) is valuable because it incorporates immunophenotype, genotype, and cytogenetics,

[**Table 118-5.** Subtypes of Non-Hodgkin Lymphoma (WHO Classification)]

but numerous other systems exist (eg, Lyon classification). Among the most important new lymphomas recognized by the WHO system are mucosa-associated lymphoid tumors (MALT—see p. 133); mantle cell lymphoma (previously diffuse small cleaved cell lymphoma); and anaplastic large cell lymphoma, a heterogeneous disorder with 75% of cases of T-cell origin, 15% of B-cell origin, and 10% unclassified. However, despite the plethora of entities, treatment is often similar except in certain T-cell lymphomas.

Lymphomas are commonly also categorized as indolent or aggressive. Indolent lymphomas are slowly progressive and responsive to therapy but are not curable with standard approaches. Aggressive lymphomas are rapidly progressive but responsive to therapy and often curable.

In children, NHL is almost always aggressive. Follicular and other indolent lymphomas are very rare. The treatment of these aggressive lymphomas (Burkitt's, diffuse large B cell, and lymphoblastic lymphoma) presents special concerns, including GI tract involvement (particularly in the terminal ileum); meningeal spread (requiring CSF prophylaxis or treatment); and other sanctuary sites of involvement (eg, testes, brain). In addition, with these potentially curable lymphomas, treatment adverse effects as well as outcome must be considered, including late risks of secondary cancer, cardiorespiratory sequelae, fertility preservation, and developmental consequences. Current research is focused on these areas as well as on the molecular events and predictors of lymphoma in children.

Symptoms and Signs

Many patients present with asymptomatic peripheral lymphadenopathy. Enlarged lymph nodes are rubbery and discrete and later become matted. Disease is localized in some patients, but most patients have several areas of involvement. Mediastinal and retroperitoneal lymphadenopathy may cause pressure symptoms on various organs. Extranodal sites may dominate clinically (eg, gastric involvement can simulate GI carcinoma; intestinal lymphoma may cause a malabsorption syndrome; HIV patients who develop NHL often present with CNS involvement).

The skin and bones are initially involved in 15% of patients with aggressive lymphoma and in 7% of those with indolent lymphoma. Occasionally, patients with extensive abdominal or thoracic disease develop chylous ascites or pleural effusion because of lymphatic obstruction. Weight loss, fever, night sweats, and asthenia indicate disseminated disease. Patients may have hepatomegaly and splenomegaly as well.

Two problems are common in NHL but rare in Hodgkin lymphoma: Congestion and edema of the face and neck from pressure on the superior vena cava (superior vena cava or superior mediastinal syndrome) may occur. Also, ureters may be compressed by retroperitoneal or pelvic lymph nodes or both; this compression may interfere with urinary flow and cause secondary renal failure.

Anemia is initially present in about 33% of patients and eventually develops in most. It may be caused by bleeding from GI lymphoma, with or without low platelet levels; hemolysis from hypersplenism or Coombs'-positive hemolytic anemia; bone marrow infiltration from lymphoma; or marrow suppression from chemotherapy or radiation therapy.

The acute illness of adult T-cell leukemia-lymphoma (associated with human T-lymphotrophic virus 1 [HTLV-1]) has a fulminating clinical course with skin infiltrates, lymphadenopathy, hepatosplenomegaly, and leukemia. The leukemic cells are malignant T cells, many with convoluted nuclei. Hypercalcemia often develops, related to humoral factors rather than to direct bone invasion.

Patients with anaplastic large cell lymphoma have rapidly progressive skin lesions, adenopathy, and visceral lesions. This disease may be mistaken for Hodgkin lymphoma or metastatic undifferentiated carcinoma.

Diagnosis

• Chest x-ray

• CT of chest, abdomen, and pelvis (possibly integrated PET-CT)

• CBC, ESR, alkaline phosphatase, LDH, liver function tests, albumin, Ca, BUN, creatinine, electrolytes, and uric acid

• HIV, hepatitis B virus, and hepatitis C virus testing

• Lymph node and bone marrow biopsy

• MRI of spine if neurologic symptoms are present

As with Hodgkin lymphoma, NHL is usually suspected in patients with painless lymphadenopathy or when mediastinal adenopathy is detected on routine chest x-ray. Painless lymphadenopathy can also result from infectious mononucleosis, toxoplasmosis, cytomegalovirus infection, primary HIV infection, or leukemia. Similar chest x-ray findings can result from lung carcinoma, sarcoidosis, or TB. Less commonly, patients present after a finding of peripheral lymphocytosis on CBC done for nonspecific symptoms. In such cases, the differential diagnosis includes leukemia, Epstein-Barr virus infection, and Duncan's syndrome (X-linked lymphoproliferative syndrome).

Chest x-ray is obtained if not done previously, and a lymph node biopsy is done if lymphadenopathy is confirmed on CT or PET scan. If only mediastinal nodes are enlarged, patients require CT-guided needle biopsy or mediastinoscopy. Usually, tests should include CBC, alkaline phosphatase, renal and liver function tests, LDH, and uric acid. Other tests are done depending on findings (eg, MRI for symptoms of spinal cord compression or CNS abnormalities).

Histologic criteria on biopsy include destruction of normal lymph node architecture and invasion of the capsule and adjacent fat by characteristic neoplastic cells. Immunophenotyping studies to determine the cell of origin are of great value in identifying specific subtypes and helping define prognosis and management; these studies also can be done on peripheral cells. Demonstration of the leukocyte common antigen CD45 by immunoperoxidase rules out metastatic cancer, which is often in the differential diagnosis of "undifferentiated" cancers. The test for leukocyte common antigen, most surface marker studies, and gene rearrangement (to document B-cell or T-cell clonality) can be done on fixed tissues. Cytogenetics and flow cytometry require fresh tissue.

Staging: Although localized NHL does occur, the disease is typically disseminated when first recognized. Staging procedures include CT of the chest, abdomen, and pelvis; PET; and bone marrow biopsy. The final staging of NHL (see Table 118-3) is similar to that of Hodgkin lymphoma and is based on clinical and pathologic findings.

Prognosis

Patients with T-cell lymphomas generally have a worse prognosis than do those with B-cell types, although newer intensive treatment regimens may lessen this difference. Prognosis for each NHL variant is related to differences in tumor cell biology.

Survival also varies with other factors. The International Prognostic Index (IPI) is frequently used in aggressive lymphomas. It considers 5 risk factors:

• Age > 60

• Poor performance status (can be measured using the Eastern Cooperative Oncology Group tool)

• Elevated LDH

• > 1 extranodal site

• Stage III or IV disease

Outcome is worse with an increasing number of risk factors. Survival, as determined by IPI factor, has improved with the addition of rituximab to the standard chemotherapeutic regimen. Patients in the highest risk groups (patients with 4 or 5 risk factors) now have a 50% 5-yr survival. Low-risk patients without any of the risk factors have a very high cure rate. A modified IPI (follicular lymphoma IPI [FLIPI]) is being used in follicular lymphomas and in diffuse large B-cell lymphoma (revised IPI [R-IPI]).

Treatment

• Chemotherapy, radiation therapy, or both

• Sometimes anti-CD20 monoclonal antibody

• Sometimes hematopoietic stem cell transplantation

Treatment varies considerably with cell type, which are too numerous to permit detailed discussion. Generalizations can be made regarding localized vs advanced disease and aggressive vs indolent forms. Burkitt's lymphoma (see below) and mycosis fungoides (see p. 1024) are discussed separately.

Localized disease (stages I and II): Patients with indolent lymphomas rarely present with localized disease, but when they do, regional radiation therapy may offer long-term control. However, relapses may occur > 10 yr after radiation therapy.

About one half of patients with aggressive lymphomas present with localized disease, for which combination chemotherapy, with or without regional radiation, is usually curative. Patients with lymphoblastic lymphomas or Burkitt's lymphoma, even if apparently localized, must receive intensive combination chemotherapy with meningeal prophylaxis. Treatment may require maintenance chemotherapy (lymphoblastic), but cure is expected.

Advanced disease (stages III and IV): For indolent lymphomas, treatment varies considerably. A watch-and-wait approach, treatment with a single alkylating drug, or 2- or 3-drug regimens may be used. Criteria considered in selecting management options include age, general health, distribution of disease, tumor bulk, histology, and anticipated benefits of therapy. The B-cell specific anti-CD20 antibody rituximab and other biologic response modifiers appear to be of benefit; one of these drugs can be combined with chemotherapy or administered as single therapy. Radiolabeled-antibody therapy is also valuable.

In patients with the aggressive B-cell lymphomas (eg, diffuse large B cell), the standard drug combination is rituximab plus cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine, prednisone (R-CHOP). Complete disease regression is expected in ≥ 70% of patients, depending on the IPI category. More than 70% of complete responders are cured, and relapses > 2 yr after treatment ceases are rare.

As cure rates have improved with the use of R-CHOP, autologous transplantation is reserved for patients with relapsed or refractory aggressive B-cell lymphomas, some younger patients with mantle cell lymphoma, and some patients with aggressive T-cell lymphomas.

Lymphoma relapse: The first relapse after initial chemotherapy is almost always treated with autologous stem cell transplantation. Patients usually should be ≤ 70 yr or in equivalent health and have responsive disease, good performance status, a source of uncontaminated stem cells, and an adequate number of CD34+ stem cells (harvested from peripheral blood or bone marrow). Consolidation myeloablative therapy may include chemotherapy with or without irradiation. Posttreatment immunotherapy (eg, rituximab, vaccination, IL-2) is being studied.

An allogeneic transplant is the donation of stem cells from a compatible donor (brother, sister, or matched unrelated donor). The stem cells have a 2-fold effect: reconstituting normal blood counts and providing a possible graft-vs-tumor effect.

In aggressive lymphoma, a cure may be expected in 30 to 50% of eligible patients undergoing myeloablative therapy.

In indolent lymphomas, cure with autologous transplantation remains uncertain, although remission may be superior to that with secondary palliative therapy alone. Reduced intensity allotransplantation appears to offer a potentially curative option in some patients with indolent lymphoma.

The mortality rate of patients undergoing myeloablative transplantation has decreased dramatically to 2 to 5% for most autologous procedures and to < 15% for most allogeneic procedures.

Complications of treatment: A late sequela of standard and high-dose chemotherapy is the occurrence of 2nd tumors, especially myelodysplasias and acute myelogenous leukemia. Chemotherapy combined with radiation therapy increases this risk, although its incidence is still only about 3%.

Burkitt's Lymphoma

Burkitt's lymphoma is a B-cell lymphoma occurring primarily in children. Endemic (African), sporadic (non-African), and immunodeficiency-related forms exist.

Burkitt's lymphoma is endemic in central Africa and constitutes 30% of childhood lymphomas in the US. The form endemic to Africa often manifests as enlargement of the jaw or facial bones. In non-African Burkitt's lymphoma, abdominal disease predominates, often arising in the region of the ileocecal valve or the mesentery. The kidneys, ovaries, or breasts may be involved as well, and in adults, disease may be bulky and generalized, often with massive involvement of liver, spleen, and bone marrow. CNS involvement is often present at diagnosis or with relapsing lymphoma.

Burkitt's lymphoma is the most rapidly growing human tumor, and pathology reveals a high mitotic rate, a monoclonal proliferation of B cells, and a "starry-sky" pattern of benign macrophages that have engulfed apoptotic malignant lymphocytes. There is a distinctive genetic translocation involving the C-*myc* gene on chromosome 8 and the immunoglobulin heavy chain of chromosome 14. The disease is closely associated with Epstein-Barr virus infection in endemic lymphoma; however, it is uncertain whether Epstein-Barr virus plays an etiologic role. Burkitt's lymphoma occurs frequently in patients with AIDS and may be an AIDS-defining disease.

Diagnosis

Diagnosis is based on biopsy of lymph node or tissue from another suspected disease site. Staging includes CT of the chest, abdomen, and pelvis, bone marrow biopsy, CSF cytology, and PET scan.

Treatment

• Intensive chemotherapy

Treatment must be initiated rapidly and staging studies must be expedited because of rapid tumor growth. An intensive alternating regimen-cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, and cytarabine (CODOX-M/IVAC)-results in a cure rate of > 90% for children and adults. Meningeal prophylaxis is essential. With treatment, tumor lysis syndrome (see p. 1075) is common, and patients must receive IV hydration, allopurinol or rasburicase, alkalinization, and close attention to electrolytes (particularly K and Ca).

If the patient presents with bowel obstruction secondary to tumor and the tumor is completely resected at initial diagnostic-therapeutic laparotomy, then aggressive therapy is still indicated. Salvage therapy for treatment failures is generally unsuccessful, underscoring the importance of very aggressive initial therapy.

Mycosis Fungoides

Mycosis fungoides is an uncommon chronic T-cell lymphoma primarily affecting the skin and occasionally the internal organs.

Mycosis fungoides is rare compared with Hodgkin lymphoma and NHL. Unlike most other lymphomas, it is insidious in onset, sometimes appearing as a chronic, pruritic rash that is difficult to diagnose. It begins focally but may spread to involve most of the skin. Lesions are plaquelike but may become nodular or ulcerated. Eventually, systemic involvement of lymph nodes, liver, spleen, and lungs occurs, resulting in the advent of symptoms, which include fever, night sweats, and unintentional weight loss.

Diagnosis

• Skin biopsy

• For staging, bone marrow biopsy and CT of chest, abdomen, and pelvis

Diagnosis is based on skin biopsy, but histology may be equivocal early in the course because of insufficient quantities of lymphoma cells. The malignant cells are mature T cells (T4+, T11+, T12+). Characteristic Pautrier's microabscesses are present in the epidermis. In some cases, a leukemic phase called Sezary syndrome is characterized by the appearance of malignant T cells with serpentine nuclei in the peripheral blood.

Once mycosis fungoides has been confirmed, the stage (see Table 118-3) is determined by CT scan of the chest, abdomen, and pelvis and by bone marrow biopsy for blood or lymph node involvement. PET scan may also be used for suspected visceral involvement.

Prognosis

Most patients are > 50 yr at diagnosis; average life expectancy is 7 to 10 yr after diagnosis, even without treatment. However, survival rates vary markedly depending on stage at diagnosis. Patients who receive treatment for stage IA disease have a life expectancy analogous to that of similar people without mycosis fungoides. Patients who receive treatment for stage IIB disease survive for about 3 yr. Patients treated for stage III disease survive an average of 4 to 6 yr. Patients treated for stage IVA or IVB disease (extra-cutaneous disease) survive < 1.5 yr.

Treatment

• Radiation therapy, topical chemotherapy, phototherapy, or topical corticosteroids

• Sometimes systemic chemotherapy

Electron beam radiation therapy, in which most of the energy is absorbed in the first 5 to 10 mm of tissue, and topical nitrogen mustard have proved highly effective. Plaques may also be treated with sunlight and topical corticosteroids. Systemic treatment with alkylating drugs and folic acid antagonists produces transient tumor regression, but systemic treatment is primarily used when other therapies have failed,

after relapse, or in patients with documented extranodal or extracutaneous disease. Extracorporeal phototherapy with a chemosensitive drug has shown modest success. The adenosine deaminase inhibitors fludarabine and 2-chlorodeoxyadenosine show promise.

Chapter 119. Plasma Cell Disorders

Introduction

(Dysproteinemias; Monoclonal Gammopathies; Paraproteinemias; Plasma Cell Dyscrasias)

Plasma cell disorders are a diverse group of disorders of unknown etiology characterized by the disproportionate proliferation of one clone of B cells and the presence of a structurally and electrophoretically homogeneous (monoclonal) immunoglobulin or polypeptide subunit in serum, urine, or both.

Patiology

(For structural features and classification of the immunoglobulins, see p. 1083.)

After developing in the bone marrow, undifferentiated B cells enter peripheral lymphoid tissues, such as lymph nodes, spleen, and Peyer's patches. Here, they begin to differentiate into cells, each of which can respond to a limited number of antigens. After encountering the appropriate antigen, some B cells undergo clonal proliferation into plasma cells. Each clonal plasma cell line is committed to synthesizing one specific immunoglobulin antibody that consists of 2 identical heavy chains (gamma [γ], mu [μ], alpha [α], delta [δ], or epsilon [ε]) and 2 identical light chains (kappa [κ] or lambda [λ]). A slight excess of light chains is normally produced, and urinary excretion of small amounts of free polyclonal light chains (≤ 40 mg/24 h) is normal.

Plasma cell disorders are of unknown etiology and are characterized by the disproportionate proliferation of one clone. The result is a corresponding increase in the serum level of its product, the monoclonal immunoglobulin protein (M-protein).

M-proteins may consist of both heavy and light chains or of only one type of chain. Some show antibody activity, which may cause autoimmune damage of organs, particularly the kidneys. When M-proteins are produced, production of other immunoglobulins is commonly reduced, and immunity may become impaired. M-protein may coat platelets, inactivate clotting factors, increase blood viscosity, and cause bleeding by other mechanisms. M-proteins may also produce secondary amyloidosis. The clonal cells can infiltrate bone matrix or marrow, with resultant osteoporosis, hypercalcemia, anemia, or pancytopenia.

Plasma cell disorders can vary from asymptomatic, stable conditions (in which only the protein is present) to progressive cancers (eg, multiple myeloma—for classification, see Table 119-1). Rarely, transient plasma cell disorders occur in patients with drug hypersensitivity (sulfonamide, phenytoin, and penicillin), with presumed viral infections, and after heart or transplant surgery.

Plasma cell disorders may be suspected because of clinical manifestations, findings during evaluation of anemia, or an incidental finding of elevated serum protein or proteinuria that leads to further evaluation with serum or urine protein electrophoresis. Electrophoresis detects M-protein, which is further evaluated with immunofixation electrophoresis for identification of heavy and light chain classes.

Heavy Chain Diseases

Heavy chain diseases are neoplastic plasma cell disorders characterized by overproduction of monoclonal immunoglobulin heavy chains. Symptoms, diagnosis, and treatment vary according to the specific disorder.

Heavy chain diseases are plasma cell disorders that are generally malignant. In most plasma cell disorders, M-proteins are structurally similar to normal antibody molecules. In contrast, in heavy chain diseases, incomplete monoclonal immunoglobulins (true paraproteins) are produced. They consist of only heavy chain components (either α, γ, μ, or δ) without light chains (ε heavy chain disease has not been described). Most heavy chain proteins are fragments of their normal counterparts with internal deletions of variable length; these deletions appear to result from structural mutations. The clinical picture is more

like lymphoma than multiple myeloma. Heavy chain diseases are considered in patients with clinical manifestations suggesting lymphoproliferative disorders.

IgA Heavy Chain Disease

(α-Chain Disease)

IgA heavy chain disease is the most common heavy chain disease and is similar to Mediterranean lymphoma (immunoproliferative small intestinal disease).

IgA heavy chain disease usually appears between ages 10 and 30 and is geographically

[**Table 119-1.** Classification of Plasma Cell Disorders]

concentrated in the Middle East. The cause may be an aberrant immune response to a parasite or other microorganism. Villous atrophy and plasma cell infiltration of the jejunal mucosa are usually present and, sometimes, infiltration of the mesenteric lymph nodes. The peripheral lymph nodes, bone marrow, liver, and spleen usually are not involved. A respiratory tract form of the disease has been reported rarely. Osteolytic lesions do not occur.

Almost all patients present with diffuse abdominal lymphoma and malabsorption. Serum protein electrophoresis is normal in half of cases; often, there is an increased α_2 and β fraction or a decreased γ fraction. Diagnosis requires the detection of a monoclonal α chain on immunofixation electrophoresis. This chain is sometimes found in concentrated urine. If it cannot be found in serum or urine, biopsy is required. The abnormal protein can sometimes be detected in intestinal secretions. The intestinal cellular infiltrate may be pleomorphic and not overtly malignant. Bence Jones proteinuria is absent.

The course is highly variable: Some patients die in 1 to 2 yr, whereas others have remissions that last many years, particularly after treatment with corticosteroids, cytotoxic drugs, and broad-spectrum antibiotics.

IgG Heavy Chain Disease

(γ-Chain Disease)

IgG heavy chain disease is generally similar to an aggressive malignant lymphoma but is occasionally asymptomatic and benign.

IgG heavy chain disease occurs primarily in elderly men but can occur in children. Associated chronic disorders include RA, Sjogren's syndrome, SLE, TB, myasthenia gravis, hypereosinophilic syndrome, autoimmune hemolytic anemia, and thyroiditis. Reductions in normal immunoglobulin levels occur. Lytic bone lesions are uncommon. Amyloidosis sometimes develops.

Common manifestations include lymphadenopathy and hepatosplenomegaly, fever, and recurring infections. Palatal edema occurs in about one fourth of patients.

The CBC may show anemia, leukopenia, thrombocytopenia, eosinophilia, and circulating atypical lymphocytes or plasma cells. Diagnosis requires demonstration by immunofixation of free monoclonal heavy chain fragments of IgG in serum and urine. Of affected patients, one half have monoclonal serum components > 1 g/dL (often broad and heterogeneous), and one half have proteinuria > 1 g/24 h. Although heavy chain proteins may involve any IgG subclass, the G3 subclass is especially common. Bone marrow or lymph node biopsy, done if other tests are not diagnostic, reveals variable histopathology.

The median survival with aggressive disease is about 1 yr. Death usually results from bacterial infection or progressive malignancy. Alkylating drugs, vincristine, or corticosteroids, and radiation therapy may yield transient remissions.

IgM Heavy Chain Disease

(μ-Chain Disease)

IgM heavy chain disease, which is rare, produces a clinical picture similar to chronic lymphocytic leukemia or other lymphoproliferative disorders.

IgM heavy chain disease most often affects adults > 50 yr. Visceral organ involvement (spleen, liver, abdominal lymph nodes) is common, but extensive peripheral lymphadenopathy is not. Pathologic fractures and amyloidosis may occur. Serum protein electrophoresis usually is normal or shows hypogammaglobulinemia. Bence Jones proteinuria (type κ) is present in 10 to 15% of patients.

Diagnosis usually requires bone marrow examination; vacuolated plasma cells are present in two thirds of patients and, when present, are virtually pathognomonic. Death can occur in a few months or in many years. The usual cause of death is uncontrollable proliferation of chronic lymphocytic leukemia cells.

Treatment depends on the patient's condition but may consist of alkylating agents plus corticosteroids or may be similar to treatment of the lymphoproliferative disorder that it most closely resembles.

Macroglobulinemia

(Primary Macroglobulinemia; Waldenstrom's Macroglobulinemia)

Macroglobulinemia is a malignant plasma cell disorder in which B cells produce excessive amounts of IgM M-proteins. Manifestations may include hyperviscosity, bleeding, recurring infections, and generalized adenopathy. Diagnosis requires bone marrow examination and demonstration of M-protein. Treatment includes plasmapheresis as needed for hyperviscosity, and systemic therapy with alkylating drugs, corticosteroids, nucleoside analogs, or monoclonal antibodies.

Macroglobulinemia, an uncommon B-cell cancer, is clinically more similar to a lymphomatous disease than to myeloma and other plasma cell disorders. Cause is unknown. Men are affected more often than women; median age is 65.

After myeloma, macroglobulinemia is the 2nd most common malignant disorder associated with a monoclonal gammopathy. Excessive amounts of IgM M-proteins can also accumulate in other disorders, causing manifestations similar to macroglobulinemia. Small monoclonal IgM components are present in the sera of about 5% of patients with B-cell non-Hodgkin lymphoma; this circumstance is termed macroglobulinemic lymphoma. Additionally, IgM M-proteins are occasionally present in patients with chronic lymphocytic leukemia or other lymphoproliferative disorders.

Clinical manifestations of macroglobulinemia may be due to the large amount of high mol wt monoclonal IgM proteins circulating in plasma, but most patients do not develop problems related to high IgM levels. Some of these proteins are antibodies directed toward autologous IgG (rheumatoid factors) or I antigens (cold agglutinins). About 10% are cryoglobulins. Secondary amyloidosis occurs in 5% of patients.

Symptoms and Signs

Most patients are asymptomatic, but many present with manifestations of hyperviscosity syndrome: fatigue, weakness, skin and mucosal bleeding, visual disturbances, headache, symptoms of peripheral neuropathy, and other changing neurologic manifestations. An increased plasma volume can precipitate heart failure. Cold sensitivity, Raynaud's syndrome, or recurring bacterial infections may occur.

Examination may disclose lymphadenopathy, hepatosplenomegaly, and purpura. Marked engorgement and localized narrowing of retinal veins, which resemble sausage links, suggests hyperviscosity syndrome. Retinal hemorrhages, exudates, microaneurysms, and papilledema occur in late stages.

Diagnosis

• CBC with platelets, RBC indices, and peripheral blood smear

• Serum protein electrophoresis followed by serum and urine immunofixation

• Serum viscosity assay

• Bone marrow examination

• Sometimes lymph node biopsy

Macroglobulinemia is suspected in patients with symptoms of hyperviscosity or other typical symptoms, particularly if anemia is present. However, it is often diagnosed incidentally when protein electrophoresis reveals an M-protein that proves to be IgM by immunofixation. Laboratory evaluation includes tests used to evaluate plasma cell disorders (see Multiple Myeloma on p. 1029) as well as measurement of cryoglobulins, rheumatoid factor, and cold agglutinins; coagulation studies; and direct Coombs' test.

Moderate normocytic, normochromic anemia, marked rouleau formation, and a very high ESR are typical. Leukopenia, relative lymphocytosis, and thrombocytopenia occasionally occur. Cryoglobulins, rheumatoid factor, or cold agglutinins may be present. If cold agglutinins are present, the direct Coombs' test usually is positive. Various coagulation and platelet function abnormalities may occur. Results of routine blood studies may be spurious if cryoglobulinemia or marked hyperviscosity is present. Normal immunoglobulins are decreased in one half of patients.

Immunofixation electrophoresis of concentrated urine frequently shows a monoclonal light chain (usually κ), but gross Bence Jones proteinuria is unusual. Bone marrow studies show a variable increase in plasma cells, lymphocytes, plasmacytoid lymphocytes, and mast cells. Periodic acid-Schiff-positive material may be present in lymphoid cells. Lymph node biopsy, done if bone marrow examination is normal, is frequently interpreted as diffuse well-differentiated or plasmacytic lymphocytic lymphoma. Serum viscosity is measured to confirm suspected hyperviscosity and when present is usually > 4.0 (normal, 1.4 to 1.8).

Treatment

• Plasmapheresis (when hyperviscosity is present)

• Alkylating drugs, nucleoside analogs, monoclonal antibodies (rituximab), or a combination

• Possibly bortezomib, thalidomide, or lenalidomide

The course is variable, with a median survival of 7 to 10 yr. Age > 60 yr, anemia, and cryoglobulinemia predict shorter survival.

Often, patients require no treatment for many years. If hyperviscosity is present, initial treatment is plasmapheresis, which rapidly reverses bleeding as well as neurologic abnormalities. Plasmapheresis often needs to be repeated.

Long-term treatment with oral alkylating drugs may be indicated for palliation, but bone marrow toxicity can occur. Nucleoside analogs (fludarabine and 2-chlorodeoxyadenosine) produce responses in large numbers of newly diagnosed patients. Rituximab can reduce tumor burden without suppressing normal hematopoiesis. However, during the first several months, IgM levels may increase, requiring plasmapheresis. The proteasome inhibitor bortezomib and the immunomodulating agents thalidomide and lenalidomide are also effective in this cancer.

Monoclonal Gammopathy of Undetermined Significance

Monoclonal gammopathy of undetermined significance (MGUS) is the production of M-protein by noncancerous plasma cells in the absence of other manifestations typical of multiple

myeloma.

The incidence of MGUS increases with age, from 1% of people aged 25 yr to > 5% of people > 70 yr. MGUS may occur in association with other disorders (see Table 119-1), in which case M-proteins may be antibodies produced in large amounts in response to protracted antigenic stimuli.

MGUS usually is asymptomatic, but peripheral neuropathy can occur. Although most cases are initially benign, up to 25% (1%/yr) progress to myeloma or a related B-cell disorder, such as macroglobulinemia, amyloidosis, or lymphoma.

Diagnosis is usually suspected when M-protein is incidentally detected in blood or urine during a routine examination. On laboratory evaluation, M-protein is present in low levels in serum (< 3 g/dL) or urine (< 300 mg/24 h). MGUS is differentiated from other plasma cell disorders because M-protein levels remain relatively stable over time and lytic bone lesions, anemia, and renal dysfunction are absent. However, patients show enhanced bone loss and a higher rate of fractures. Thus, baseline evaluation with a skeletal survey and bone densitometry should be done. Bone marrow shows only mild plasmacytosis (< 10% of nucleated cells).

No antineoplastic treatment is recommended. However, recent studies suggest that MGUS patients with associated bone loss (osteopenia or osteoporosis) may benefit from treatment with bisphosphonates. Patients should be evaluated for progression of disease every 6 to 12 mo with clinical examination and serum and urine protein electrophoresis.

Multiple Myeloma

(Myelomatosis; Plasma Cell Myeloma)

Multiple myeloma is a cancer of plasma cells that produce monoclonal immunoglobulin and invade and destroy adjacent bone tissue. Common manifestations include bone pain, renal insufficiency, hypercalcemia, anemia, and recurrent infections. Diagnosis requires demonstration of M-protein (sometimes present in urine and not serum) and either lytic bone lesions, light-chain proteinuria, or excessive plasma cells in bone marrow. A bone marrow biopsy is usually needed. Specific treatment includes conventional chemotherapy with the addition of bortezomib, lenalidomide, thalidomide, corticosteroids, and high-dose melphalan followed by autologous peripheral blood stem cell transplantation.

The incidence of multiple myeloma is 2 to 4/100,000. Male:female ratio is 1.6:1, and the median age is about 65 yr. Prevalence in blacks is twice that in whites. Etiology is unknown, although chromosomal and genetic factors, radiation, and chemicals have been suggested.

Pathophysiology

The M-protein produced by the malignant plasma cells is IgG in about 55% of myeloma patients and IgA in about 20%; of patients producing either IgG or IgA, 40% also have Bence Jones proteinuria, which is free monoclonal κ or λ light chains in the urine. In 15 to 20% of patients, plasma cells secrete only Bence Jones protein. IgD myeloma accounts for about 1% of cases.

Diffuse osteoporosis or discrete osteolytic lesions develop, usually in the pelvis, spine, ribs, and skull. Lesions are caused by bone replacement by expanding plasmacytomas or by cytokines that are secreted by malignant plasma cells that activate osteoclasts and suppress osteoblasts. The osteolytic lesions are usually multiple; occasionally, they are solitary intramedullary masses. Enhanced bone loss may also lead to hypercalcemia. Extraosseous solitary plasmacytomas are unusual but may occur in any tissue, especially in the upper respiratory tract.

Renal failure (myeloma kidney) occurs in many patients at diagnosis or during the course of the disorder due to many causes, most commonly from deposition of light chains in the distal tubules and hypercalcemia. Patients also often develop anemia usually from kidney disease or suppression of erythropoiesis by cancer cells.

Susceptibility to bacterial infection may occur in some patients. Viral infections, especially herpes infections, are increasingly occurring as a result of newer treatment modalities. Secondary amyloidosis (see p. 906) occurs in 10% of myeloma patients, most often in patients with Bence Jones proteinuria of λ-type.

Variant expressions of multiple myeloma occur (see Table 119-2).

[**Table 119-2.** Variant Expressions of Multiple Myeloma]

Symptoms and Signs

Persistent bone pain (especially in the back or thorax), renal failure, and recurring bacterial infections are the most common problems on presentation, but many patients are identified when routine laboratory tests show an elevated total protein level in the blood or show proteinuria. Pathologic fractures are common, and vertebral collapse may lead to spinal cord compression and paraplegia. Symptoms of anemia predominate or may be the sole reason for evaluation in some patients, and a few patients have manifestations of hyperviscosity syndrome (see p. 1027). Peripheral neuropathy, carpal tunnel syndrome, abnormal bleeding, and symptoms of hypercalcemia (eg, polydipsia) are common. Patients may also present with renal failure. Lymphadenopathy and hepatosplenomegaly are unusual.

Diagnosis

- CBC with platelets, peripheral blood smear, ESR, and chemistry panel (BUN, creatinine, Ca, uric acid, LDH)
- Serum and urine protein electrophoresis followed by immunofixation
- X-rays (skeletal survey)
- Bone marrow examination

Multiple myeloma is suspected in patients > 40 yr with persistent unexplained bone pain, particularly at night or at rest, other typical symptoms, or unexplained laboratory abnormalities, such as elevated blood protein or urinary protein, hypercalcemia, renal insufficiency, or anemia. Laboratory evaluation includes routine blood tests, protein electrophoresis, x-rays, and bone marrow examination.

Routine blood tests include CBC, ESR, and chemistry panel. Anemia is present in 80% of patients, usually normocytic-normochromic anemia with formation of rouleau, which are clusters of 3 to 12 RBCs that occur in stacks. WBC and platelet counts are usually normal. ESR usually is > 100 mm/h; BUN, serum creatinine, LDH, and serum uric acid are frequently elevated. Anion gap is sometimes low. Hypercalcemia is present at diagnosis in about 10% of patients.

Protein electrophoresis is done on a serum sample and on a urine sample concentrated from a 24-h collection to quantify the amount of urinary M-protein. Serum electrophoresis identifies M-protein in about 80 to 90% of patients. The remaining 10 to 20% are usually patients with only free monoclonal light chains (Bence Jones protein) or IgD. They almost always have M-protein detected by urine protein electrophoresis. Immunofixation electrophoresis can identify the immunoglobulin class of the M-protein and can often detect light-chain protein if serum immuno-electrophoresis is falsely negative; immunofixation electrophoresis is done even when the serum test is negative if multiple myeloma is strongly suspected. Light-chain analysis with delineation of κ and λ ratios helps confirm the diagnosis. Light-chain analysis can also be used to monitor efficacy of therapy and provide prognostic data. Serum level of β_2-microglobulin is measured if diagnosis is confirmed or very likely; it frequently is elevated, and albumin may be decreased. A new international staging system uses the levels of serum albumin and β_2-microglobulin to indicate severity of disease and subsequent prognosis.

X-rays include a skeletal survey. Punched-out lytic lesions or diffuse osteoporosis is present in 80% of

cases. Radionuclide bone scans usually are not helpful. MRI can provide more detail and is obtained if specific sites of pain or neurologic symptoms are present.

Bone marrow aspiration and biopsy are done and reveal sheets or clusters of plasma cells; myeloma is diagnosed when > 10% of the cells are of this type. However, bone marrow involvement is patchy; therefore, some samples from patients with myeloma may show < 10% plasma cells. Still, the number of plasma cells in bone marrow is rarely normal. Plasma cell morphology does not correlate with the class of immunoglobulin synthesized. Chromosomal studies on bone marrow may reveal specific karyotypic abnormalities in plasma cells associated with differences in survival.

In patients without serum M protein, myeloma is indicated by Bence Jones proteinuria > 300 mg/24 h, osteolytic lesions (without evidence of metastatic cancer or granulomatous disease), and sheets or clusters of plasma cells in the bone marrow.

Prognosis

The disease is progressive and incurable, but median survival has recently improved to > 5 yr as a result of advances in treatment. Unfavorable prognostic signs at diagnosis are lower serum albumin and higher β_2-microglobulin levels. Patients presenting with renal failure also do poorly unless kidney function improves with therapy.

Because multiple myeloma is ultimately fatal, patients are likely to benefit from discussions of end-of-life care that involve their doctors and appropriate family and friends. Points for discussion may include advance directives, the use of feeding tubes, and pain relief.

Treatment

• Chemotherapy for symptomatic patients

• Thalidomide, bortezomib, or lenalidomide with corticosteroids and/or chemotherapy

• Possibly maintenance therapy

• Possibly stem cell transplantation

• Possibly radiation therapy

• Treatment of complications (anemia, hypercalcemia, renal insufficiency, infections, skeletal lesions)

Treatment of myeloma has improved in the past decade, and long-term survival is a reasonable therapeutic target. Therapy involves direct treatment of malignant cells in symptomatic patients and the treatment of the complications. Asymptomatic patients probably do not benefit from treatment, which is usually withheld until symptoms or complications develop. However, patients with evidence of lytic lesions or bone loss (osteopenia or osteoporosis) should be treated with monthly infusions of zoledronic acid or pamidronate to reduce the risk of skeletal complications.

Treatment of malignant cells: Until recently, conventional chemotherapy consisted only of oral melphalan and prednisone given in cycles of 4 to 6 wk with monthly evaluation of response. Recent studies show superior outcome with the addition of either bortezomib or thalidomide. Other chemotherapeutic drugs, including other alkylating drugs (eg, cyclophosphamide, doxorubicin and its newer analog liposomal pegylated doxorubicin) also are more effective when combined with thalidomide or bortezomib. Many other patients are effectively treated with bortezomib, thalidomide, or lenalidomide plus glucocorticoids and/or chemotherapy.

Chemotherapy response is indicated by decreases in serum or urine M-protein, increases in RBCs, and improvement in renal function among patients presenting with kidney failure.

Autologous peripheral blood stem cell transplantation may be considered for patients who have adequate

cardiac, hepatic, pulmonary, and renal function, particularly those whose disease is stable or responsive after several cycles of initial therapy. Allogeneic stem cell transplantation after nonmyeloablative chemotherapy (eg, low-dose cyclophosphamide and fludarabine) or low-dose radiation therapy can produce myeloma-free survival of 5 to 10 yr in some patients. However, allogeneic stem cell transplantation remains experimental because of the high morbidity and mortality from graft vs. host disease.

In relapsed or refractory myeloma, combinations of bortezomib, thalidomide, or its newer analog lenalidomide with chemotherapy or corticosteroids may be used. These drugs are usually combined with other effective drugs that the patient has not yet been treated with, although patients with prolonged remissions may respond to retreatment with the same regimen that led to the remission.

Maintenance therapy has been tried with nonchemotherapeutic drugs, including interferon alfa, which prolongs remission but does not improve survival and is associated with significant adverse effects. Following a response to corticosteroid-based regimens, corticosteroids alone are effective as a maintenance treatment. Thalidomide may also be effective as a maintenance treatment, and studies are evaluating maintenance therapy with bortezomib and lenalidomide among patients who have responded to these drugs alone or in combination therapeutic regimens.

Treatment of complications: In addition to direct treatment of malignant cells, therapy must also be directed at complications, which include anemia, hypercalcemia, renal insufficiency, infections, and skeletal lesions.

Anemia can be treated with recombinant erythropoietin (40,000 units sc once/wk) in patients whose anemia is inadequately relieved by chemotherapy. If anemia causes cardiovascular or significant systemic symptoms, packed RBCs are transfused. Plasmapheresis is indicated if hyperviscosity develops (see p. 1027).

Hypercalcemia is treated with saluresis, IV bisphosphonates, and sometimes with prednisone. Most patients do not require allopurinol. However, allopurinol is indicated for patients with high levels of serum uric acid or high tumor burden and a high risk of tumor lysis syndrome with treatment.

Renal compromise can be ameliorated with adequate hydration. Even patients with prolonged, massive Bence Jones proteinuria (≥ 10 to 30 g/day) may have intact renal function if they maintain urine output > 2000 mL/day. Dehydration combined with high-osmolar IV contrast may precipitate acute oliguric renal failure in patients with Bence Jones proteinuria.

Infection is more likely during chemotherapy-induced neutropenia. In addition, infections with the herpes zoster virus are occurring more frequently in patients treated with newer antimyeloma drugs. Documented bacterial infections should be treated with antibiotics; however, prophylactic use of antibiotics is not routinely recommended. Prophylactic use of antiviral drugs may be indicated for patients receiving specific drugs. Prophylactic IV immune globulin may reduce the risk of infection but is generally reserved for patients with recurring infections. Pneumococcal and influenza vaccines are indicated to prevent infection.

Skeletal lesions require multiple supportive measures. Maintenance of ambulation and supplemental Ca and vitamin D help preserve bone density. Analgesics and palliative doses of radiation therapy (18 to 24 Gy) can relieve bone pain. However, radiation therapy may impair the patient's ability to receive cytotoxic doses of systemic chemotherapy. Most patients, especially those with lytic lesions and generalized osteoporosis or osteopenia, should receive a monthly IV bisphosphonate (either pamidronate or zoledronic acid). Bisphosphonates reduce skeletal complications and lessen bone pain and may have an antitumor effect.

Chapter 120. Iron Overload

Introduction

(Hemosiderosis; Hemochromatosis)

(For iron poisoning, see p. 3341.)

Iron (Fe) in excess of bodily needs is deposited in tissues:

- Hemosiderosis is focal deposition of iron that does not cause tissue damage.
- Hemochromatosis (iron overload) is a typically systemic process in which iron deposition can cause tissue damage.

Iron overload may result from primary hemochromatosis (a genetic disorder of iron metabolism), from excess oral intake or absorption of iron, or from repeated blood transfusions. Morbidity is mainly due to iron accumulation in the endocrine organs (especially the pancreas, gonads, and pituitary), liver, and heart.

Hemosiderosis

Hemosiderosis is focal deposition of iron that does not cause tissue damage.

Focal hemosiderosis can result from hemorrhage within an organ. Iron liberated from extravasated RBCs is deposited within that organ, and significant hemosiderin deposits may eventually develop. Occasionally, iron loss from tissue hemorrhage causes iron deficiency anemia, because iron in tissues cannot be reused.

Usually the lungs are affected, and the cause usually is recurrent pulmonary hemorrhage, either idiopathic (eg, Goodpasture's syndrome) or due to chronic pulmonary hypertension (eg, from primary pulmonary hypertension, pulmonary fibrosis, severe mitral stenosis).

Another common site of accumulation is the kidneys, where hemosiderosis can result from extensive intravascular hemolysis (see p. 934). Free Hb is filtered at the glomerulus, resulting in iron deposition in the kidneys. The renal parenchyma is not damaged, but severe hemosiderinuria may result in iron deficiency.

Primary Hemochromatosis

(Hereditary Hemochromatosis)

Primary hemochromatosis is a genetic disorder characterized by excessive iron accumulation that results in tissue damage. Manifestations can include constitutional symptoms, liver disorders, cardiomyopathy, diabetes, erectile dysfunction, and arthropathy. Diagnosis is by serum ferritin level and gene assay. Treatment is usually with serial phlebotomies.

Etiology

Until recently, the cause in virtually all patients with primary hemochromatosis was thought to be a mutation of the *HFE* gene. Recently, other causes have been identified; different mutations causing primary hemochromatosis occur in ferroportin disease, juvenile hemochromatosis, neonatal hemochromatosis (neonatal iron storage disease), hypotransferrinemia, and aceruloplasminemia. Although these types vary markedly in age of onset, clinical consequences of iron overload are the same in all.

More than 80% of *HFE*-related hemochromatosis is caused by the homozygous *C282Y* or *C282Y/H63D*

compound heterozygote mutation. The disorder is autosomal recessive, with a homozygous frequency of 1:200 and a heterozygous frequency of 1:8 in people of northern European ancestry. It is uncommon among blacks and rare among people of Asian ancestry. Of patients with clinical hemochromatosis, 83% are homozygous. However, for unknown reasons, phenotypic (clinical) disease is much less common than predicted by the frequency of the gene (ie, many homozygous people do not manifest the disorder).

Pathophysiology

Normal total body iron content is about 2.5 g in women and 3.5 g in men. Because symptoms may be delayed until iron accumulation is excessive, hemochromatosis may not be recognized until total body iron content is > 10 g, or often several times greater. In women, clinical manifestations are uncommon before menopause because iron loss due to menses (and sometimes pregnancy and childbirth) tends to offset iron accumulation.

The mechanism for iron overload is increased iron absorption from the GI tract, leading to chronic deposition of iron in the tissues. Hepcidin, a liver-derived peptide, is the critical control mechanism for iron absorption. Hepcidin, along with the normal *HFE* gene, prevents excessive iron absorption and storage in normal people.

In general, tissue injury appears to result from reactive free hydroxyl radicals generated when iron deposition in tissues catalyzes their formation. Other mechanisms may affect particular organs (eg, skin hyperpigmentation can result from increased melanin as well as iron accumulation).

Symptoms and Signs

The clinical consequences of iron overload are the same regardless of the etiology and pathophysiology of the overload.

Historically, experts believed that symptoms did not develop until significant organ damage had occurred. However, organ damage is slow and subtle, and fatigue and nonspecific constitutional symptoms often occur early.

Other symptoms relate to the organs with the largest iron deposits (see Table 120-1). In men, the initial symptoms may be hypogonadism and erectile dysfunction caused by gonadal iron deposition. Glucose intolerance or diabetes mellitus is another common initial presentation. Some patients present with hypothyroidism.

Liver disease is the most common complication and may progress to cirrhosis; 20 to 30% of patients with cirrhosis develop hepatocellular carcinoma. Liver disease is the most common cause of death. Cardiomyopathy with heart failure is the 2nd most common fatal complication. Hyperpigmentation (bronze diabetes) is common, as is symptomatic arthropathy.

[**Table 120-1.** Common Manifestations of Primary Hemochromatosis]

Diagnosis

• Serum ferritin level

• Genetic testing

Symptoms and signs may be nonspecific, subtle, and of gradual onset, so that index of suspicion should be high. Primary hemochromatosis should be suspected when typical manifestations, particularly combinations of such manifestations, remain unexplained after routine evaluation. Although any family history is a more specific clue, it is not usually present.

Serum ferritin measurement is the simplest and most direct initial test. Elevated levels (> 200 ng/mL in women or > 300 ng/mL in men) are usually present in primary hemochromatosis but can result from other abnormalities, such as inflammatory liver disorders (eg, chronic viral hepatitis, nonalcoholic

steatohepatitis, alcoholic liver disease), cancer, certain systemic inflammatory disorders (eg, RA, hemophagocytic lymphohistiocytosis), or obesity. Further testing is done if ferritin level is abnormal; testing includes serum iron (usually > 300 mg/dL) and iron binding capacity (transferrin saturation; levels usually > 50%). Gene assay is diagnostic of primary hemochromatosis caused by *HFE* gene mutations. Other types of primary hemochromatosis (eg, ferroportin disease, juvenile hemochromatosis, neonatal hemochromatosis, transferrin deficiency, ceruloplasmin deficiency) are suspected in very rare instances in which ferritin and iron blood tests indicate iron overload and genetic testing is negative for the *HFE* gene mutation, particularly in younger patients. Confirmation of these diagnoses is evolving.

Because the presence of cirrhosis affects prognosis, a liver biopsy is commonly done and tissue iron content is measured (when available). High-intensity MRI is a noninvasive alternative for estimating hepatic iron content that is becoming increasingly accurate.

Screening is required for first-degree relatives of people with primary hemochromatosis by measuring serum ferritin levels and testing for the *282Y/H63D* gene.

Treatment

• Phlebotomy

Treatment is indicated for patients with clinical manifestations, elevated serum ferritin levels (particularly levels > 1000 ng/mL), or elevated transferrin saturation. Asymptomatic patients need only periodic (eg, yearly) clinical evaluation and measurement of serum iron, ferritin, and transferrin saturation.

Phlebotomy is the simplest and most effective method to remove excess iron. It delays progression of fibrosis to cirrhosis, sometimes even reversing cirrhotic changes, and prolongs survival, but it does not prevent hepatocellular carcinoma. About 500 mL of blood (about 250 mg of iron) is removed weekly until serum iron levels are normal and transferrin saturation is < 50%. Weekly phlebotomy may be needed for many months (eg, if 250 mg Fe are removed per week, 40 wk will be required to remove 10 g Fe). When iron levels are normal, phlebotomies can be intermittent to maintain transferrin saturation at < 30%.

Diabetes, cardiomyopathy, erectile dysfunction, and other secondary manifestations are treated as indicated.

Patients should follow a balanced diet; it is not necessary to restrict consumption of iron-containing foods (eg, red meat, liver). Alcohol should be consumed only in moderation because it can increase iron absorption and, in high amounts, increases the risk of cirrhosis.

Ferroportin Disease

Ferroportin disease occurs largely in people of southern European ancestry. It results from an autosomal dominant mutation in the *SLC 40 A1* gene. It manifests in the first decade of life as increased serum ferritin levels with low or normal transferrin saturation; progressive saturation of transferrin occurs when patients are in their 20s and 30s. Clinical manifestations are milder than in *HFE* disease, with modest liver disease and mild anemia. Tolerance to vigorous phlebotomy is poor; serial monitoring of Hb level and transferrin saturation is required.

Juvenile Hemochromatosis

Juvenile hemochromatosis is a rare autosomal recessive disorder caused by mutations in the *HJV* gene that affect the transcription protein hemojuvelin. It often manifests in adolescents. Symptoms and signs include progressive hepatomegaly and hypogonadotropic hypogonadism. Ferritin levels are > 1000 ng/mL, and transferrin saturation is > 90%.

Transferrin and Ceruloplasmin Deficiency

(Hypotransferrinemia/Atransferrinemia; Aceruloplasminemia)

In transferrin deficiency, absorbed iron that enters the portal system not bound to transferrin is deposited in the liver. Subsequent iron transfer to sites of RBC production is reduced because of transferrin deficiency.

In ceruloplasmin deficiency, lack of ferroxidase causes defective conversion of Fe^{2+} to Fe^{3+}; such conversion is necessary for binding to transferrin. Defective transferrin binding impairs the movement of iron from intracellular stores to plasma transport, resulting in accumulation of iron in tissues.

Diagnosis is based on measurement of serum transferrin (ie, iron-binding capacity) and ceruloplasmin levels (see Inherited Copper Toxicity on p. 51). Treatment is experimental; eg, iron chelators may be better tolerated than phlebotomy because patients typically have anemia.

Transferrin Receptor 2 Mutation

Mutations in transferrin receptor 2, a protein that appears to control saturation of transferrin, can cause a rare autosomal recessive form of hemochromatosis. Symptoms and signs are similar to *HFE* hemochromatosis.

Secondary Iron Overload

(Secondary Hemochromatosis)

Secondary iron overload results from excess absorption of iron, repeated blood transfusions, or excess oral intake, typically in patients with disorders of erythropoiesis. Diagnosis is with serum iron studies. Treatment is usually by iron chelation.

Etiology

Secondary iron overload typically occurs in patients who have

- Hemoglobinopathies (eg, sickle cell disease, thalassemia, sideroblastic anemias)
- Congenital hemolytic anemias
- Myelodysplasia

Iron overload results from the following mechanisms:

- Increased iron absorption (which occurs, for unknown reasons, with ineffective erythropoiesis)
- Exogenous iron given to treat the anemia
- Repeated blood transfusions (each unit of blood provides about 250 mg of iron; tissue deposition becomes significant when more than about 40 units of blood are transfused)

Patients with hemoglobinopathies and congenital hemolytic anemias now typically live into adulthood, so complications of iron overload are now common. In such patients, iron overload involving the heart, the liver, and endocrine organs has become a common cause of death, but survival can be prolonged by iron removal.

Diagnosis

Patients with ineffective erythropoiesis should be evaluated for secondary iron overload, which is diagnosed by measuring serum ferritin, serum iron, and transferrin saturation.

Treatment

- Usually iron chelation with deferasirox or deferoxamine

Some patients can be treated with phlebotomy and given erythropoietin to maintain erythropoiesis. However, because it worsens anemia, phlebotomy is not recommended for many patients (eg, those with Hb level < 10 g/dL, those who are transfusion dependent, and those who develop symptoms of anemia after phlebotomy). Treatment in these patients is iron chelation. The goal of treatment is a transferrin saturation of < 50%.

Deferoxamine is the drug traditionally used for iron chelation therapy. It is given by a slow subcutaneous infusion overnight through a portable pump for 5 to 7 nights/wk or via 24-h IV infusion. Dose is 1 to 2 g in adults and 20 to 40 mg/kg in children. However, this therapy is complex to administer and requires an unusual time commitment from patients, resulting in a high rate of nonadherence. Important adverse effects include hypotension, GI disturbances, and anaphylaxis (acutely) and vision and hearing loss (with chronic use).

Deferasirox, an oral chelating agent, is an effective and increasingly used alternative to deferoxamine. Deferasirox reduces iron levels and prevents or delays onset of complications of iron overload. Initial dose is 20 mg/kg po once/day. Patients are monitored monthly with dose increases of up to 30 mg/kg once/day. Treatment can be interrupted when serum ferritin is < 500 ng/mL. Adverse effects (which occur in about 10% of patients) can include nausea, abdominal pain, diarrhea, and rash. Liver and kidney function may become abnormal; liver and kidney function tests should be done periodically (eg, monthly, sometimes more frequently for high-risk patients).

Chapter 121. Transfusion Medicine

Introduction

More than 29 million units of blood components are transfused yearly in the US, from about 8 million volunteer donors. Although transfusion is probably safer than ever, risk (and the public's perception of risk) mandates informed consent whenever practical.

Blood Collection

In the US, the collection, storage, and transport of blood and its components are standardized and regulated by the FDA, the AABB, and sometimes state or local health authorities. Donor screening includes an extensive questionnaire and health interview; measurement of temperature, heart rate, and BP; and Hb determination. Some potential donors are deferred either temporarily or permanently (see Table 121-1). Criteria for deferral protect prospective donors from possible ill effects of donation and recipients from disease. Donations are limited to once every 56 days. With rare exceptions, blood donors are unpaid.

In standard blood donation, about 450 mL of whole blood is collected in a plastic bag containing an anticoagulant preservative. Whole blood or packed RBCs preserved with citrate-phosphate-dextrose-adenine may be stored for 35 days. Packed RBCs may be stored for 42 days if an adenine-dextrose-saline solution is added.

[**Table 121-1.** Some Reasons for Blood Donation Deferral or Denial]

Autologous donation, which is use of the patient's own blood, is the preferred method of transfusion when conditions permit. In the 2 to 3 wk preceding elective surgery, up to 3 or 4 units of whole blood or packed RBCs are collected, and the patient is given iron supplements. Special blood salvage procedures are also available for collecting and autotransfusing blood shed after trauma and during surgery.

Pretransfusion Testing

Donor blood testing includes ABO and Rh_0(D) antigen typing, antibody screening, and testing for infectious disease markers (see Table 121-2).

Compatibility testing tests the recipient's RBCs for antigens A, B, and Rh_0(D); screens the recipient's plasma for antibodies against other RBC antigens; and includes a cross-match to ensure that the recipient's plasma is compatible with antigens on donor RBCs. Compatibility testing is done before a transfusion; however, in an emergency, testing is done after releasing blood from the blood bank. It can also help in diagnosing transfusion reactions.

ABO typing of donor and recipient blood is done to prevent transfusion of incompatible RBCs (see Fig. 121-1). As a rule, blood for transfusion should be of the same ABO type as that of the recipient. In urgent situations or when the correct ABO type is in doubt or unknown, type O Rh-negative packed RBCs (not whole blood—see p. 1040 for Acute Hemolytic Transfusion Reaction), which contains neither A nor B antigens, may be used for patients of any ABO type.

Rh typing determines whether the Rh factor Rh_0(D) is present on (Rh-positive) or absent from (Rh-negative) the RBCs. Rh-negative patients should always receive Rh-negative blood except in life-threatening emergencies when Rh-negative blood is unavailable. Rh-positive patients may receive Rh-positive or Rh-negative blood. Occasionally, RBCs from some Rh-positive people react weakly on standard Rh typing (weak D, or D^u, positive), but these people are still considered Rh-positive.

Antibody screening for unexpected anti-RBC antibodies is routinely done on blood from prospective recipients and prenatally on maternal specimens. Unexpected anti-RBC antibodies are specific for RBC blood group antigens other than A and B [eg, Rh_0(D), Kell (K), Duffy (Fy)]. Early detection is important,

because such antibodies can cause serious

[**Table 121-2.** Infectious Disease Transmission Testing]

[**Fig. 121-1.** Compatible RBC types.]

hemolytic transfusion reactions or hemolytic disease of the newborn (see p. 2784), and they may greatly complicate compatibility testing and delay procurement of compatible blood.

Indirect antiglobulin testing (the indirect Coombs' test) is used to screen for unexpected anti-RBC antibodies. This test may be positive in the presence of an unexpected blood group antibody or when free (non-RBC-attached) antibody is present in autoimmune hemolytic anemias (see p. 936). Reagent RBCs are mixed with the patient's serum, incubated, washed, tested with antihuman globulin, and observed for agglutination. Once an antibody is detected, its specificity is determined. Knowing the specificity of the antibody is helpful for assessing its clinical significance, selecting compatible blood, and managing hemolytic disease of the newborn.

Direct antiglobulin testing (the direct Coombs' test) detects antibodies that have coated the patient's RBCs in vivo. It is used when immune-mediated hemolysis is suspected. Patients' RBCs are directly tested with antihuman globulin and observed for agglutination. A positive result, if correlated with clinical findings, suggests autoimmune hemolytic anemia, drug-induced hemolysis, a transfusion reaction, or hemolytic disease of the newborn.

Antibody titration is done when a clinically significant, unexpected anti-RBC antibody is identified in the serum of a pregnant woman or in a patient with cold autoimmune hemolytic anemia (see p. 936). The maternal antibody titer correlates fairly well with the severity of hemolytic disease in the incompatible fetus and is often used to guide treatment in hemolytic disease of the newborn along with ultrasonography and amniotic fluid study.

The addition of a cross-match to ABO/Rh typing and antibody screening increases detection of incompatibility by only 0.01%. If the recipient has a clinically significant anti-RBC antibody, donor blood is restricted to RBC units negative for the corresponding antigen; further testing for compatibility is done by combining recipient serum, donor RBCs, and antihuman globulin. In recipients without clinically significant anti-RBC antibodies, an immediate spin cross-match, which omits the antiglobulin phase, confirms ABO compatibility.

Emergency transfusion is done when not enough time (generally < 60 min) is available for thorough compatibility testing because the patient is in hemorrhagic shock. When time permits (about 10 min is needed), ABO/Rh type-specific blood may be given. In more urgent circumstances, type O RBCs are transfused if the ABO type is uncertain, and Rh-negative blood is given if the Rh type is uncertain.

"Type and screen" may be requested in circumstances not likely to require transfusion, as in elective surgery. The patient's blood is typed for ABO/Rh antigens and screened for antibodies. If antibodies are absent and the patient needs blood, ABO/Rh type specific or compatible RBCs may be released without the antiglobulin phase of the cross-match. If an unexpected antibody is present, full testing is required.

Blood Products

Whole blood can provide improved O_2-carrying capacity, volume expansion, and replacement of clotting factors and was previously recommended for rapid massive blood loss. However, because component therapy is equally effective and is a more efficient use of donated blood, whole blood is not generally available in the US.

RBCs: Packed RBCs are ordinarily the component of choice with which to increase Hb. Indications depend on the patient. O_2-carrying capacity may be adequate with Hb levels as low as 7 g/L in healthy patients, but transfusion may be indicated with higher Hb levels in patients with decreased cardiopulmonary reserve or ongoing bleeding. One unit of RBCs increases an average adult's Hb by

about 1 g/dL, and the Hct by about 3% above the pretransfusion Hct value. When only volume expansion is required, other fluids can be used concurrently or separately. In patients with multiple blood group antibodies or with antibodies to high-frequency RBC antigens, rare frozen RBCs are used.

Washed RBCs are free of almost all traces of plasma, most WBCs, and platelets. They are generally given to patients who have severe reactions to plasma (eg, severe allergies, paroxysmal nocturnal hemoglobinuria, or IgA immunization). In IgA-immunized patients, blood collected from IgA-deficient donors may be preferable for transfusion.

WBC-depleted RBCs are prepared with special filters that remove ≥ 99.99% of WBCs. They are indicated for patients who have experienced nonhemolytic febrile transfusion reactions, for exchange transfusions, for patients who require cytomegalovirus-negative blood that is unavailable, and possibly for the prevention of platelet alloimmunization.

Fresh frozen plasma: Fresh frozen plasma (FFP) is an unconcentrated source of all clotting factors without platelets. Indications include correction of bleeding secondary to factor deficiencies for which specific factor replacements are unavailable, multifactor deficiency states (eg, massive transfusion, disseminated intravascular coagulation [DIC], liver failure), and urgent warfarin reversal, although prothrombin complex concentrate (PCC) should be the first choice if available. FFP can supplement RBCs when whole blood is unavailable for exchange transfusion. FFP should not be used simply for volume expansion.

Cryoprecipitate: Cryoprecipitate is a concentrate prepared from FFP. Each concentrate usually contains about 80 units each of factor VIII and von Willebrand's factor and about 250 mg of fibrinogen. It also contains fibronectin and factor XIII. Although originally used for hemophilia and von Willebrand's disease, cryoprecipitate is currently used as a source of fibrinogen in acute DIC with bleeding, treatment of uremic bleeding, cardiothoracic surgery (fibrin glue), obstetric emergencies such as abruptio placentae and HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, and rare factor XIII deficiency. In general, it should not be used for other indications.

WBCs: Granulocytes may be transfused when sepsis occurs in a patient with profound persistent neutropenia (WBCs < 500/μL) who is unresponsive to antibiotics. Granulocytes must be given within 24 h of harvest; however, testing for HIV, hepatitis, human T-cell lymphotropic virus, and syphilis may not be completed before infusion. Because of improved antibiotic therapy and drugs that stimulate granulocyte production during chemotherapy, granulocytes are seldom used.

Immune globulins: Rh immune globulin (RhIg), given IM or IV, prevents development of maternal Rh antibodies that can result from fetomaternal hemorrhage. The standard dose of intramuscular RhIg (300 μg) must be given to an Rh-negative mother immediately after abortion or delivery (live or stillborn) unless the infant is $Rh_0(D)$ and D^u negative or the mother's serum already contains anti-$Rh_0(D)$. If fetomaternal hemorrhage is > 30 mL, a larger dose is needed. If hemorrhage of this amount is suspected, testing of the volume of fetomaternal hemorrhage begins with the screening rosette test, which, if positive, is followed by a quantitative test (eg, Kleihauer-Betke). RhIg is given IV only when IM administration is contraindicated (eg, in patients with coagulopathy).

Other immune globulins are available for postexposure prophylaxis for patients exposed to a number of infectious diseases, including cytomegalovirus, hepatitis A and B, measles, rabies, respiratory syncytial virus, rubella, tetanus, smallpox, and varicella (for usage, see under specific disease).

Platelets: Platelet concentrates are used to prevent bleeding in asymptomatic severe thrombocytopenia (platelet count < 10,000/μL), for bleeding patients with less severe thrombocytopenia (platelet count < 50,000/μL), for bleeding patients with platelet dysfunction due to antiplatelet drugs but with normal platelet count, for patients receiving massive transfusion that causes dilutional thrombocytopenia, and sometimes before invasive surgery, particularly with extracorporeal circulation for > 2 h (which often makes platelets dysfunctional). One platelet concentrate unit increases the platelet count by about 10,000/μL, and adequate hemostasis is achieved with a platelet count of about 10,000/μL in a patient without complicating conditions and about 50,000/μL for those undergoing surgery. Therefore, 4 to 6 units

of random donor platelet concentrates are commonly used in adults.

Platelet concentrates are increasingly being prepared by automated devices that harvest the platelets (or other cells) and return unneeded components (eg, RBCs, plasma) to the donor. This procedure, called cytapheresis, provides enough platelets from a single donation (equivalent to 6 random platelet units) for transfusion to an adult, which, because it minimizes infectious and immunogenic risks, is preferred to multiple donor transfusions in certain conditions.

Certain patients may not respond to platelet transfusions, possibly because of splenic sequestration or platelet consumption due to HLA or platelet-specific antigen alloimmunization. These patients may respond to multiple random donor platelets (because of greater likelihood that some units are HLA compatible), platelets from family members, or ABO-or HLA-matched platelets. Alloimmunization may be mitigated by transfusing WBC-depleted RBCs and WBC-depleted platelet concentrates.

Other products: Irradiated blood products are used to prevent graft-vs-host disease in patients at risk (see p. 1042). Blood substitutes are being developed that use inert chemicals or Hb solutions to carry and deliver O_2 to tissues. Perfluorocarbons are chemically and biologically inactive and are capable of dissolving O_2 and CO_2 under pressure. Because perfluorocarbons are not water miscible, they are prepared as emulsions. They are undergoing phase II and III clinical trials. Hb-based O_2 carrier solutions are undergoing phase III clinical trials in the US. Hb, human or bovine, is chemically modified, producing a solution capable of O_2 transport. These solutions can be stored at room temperature for up to 2 yr, making them attractive for transport to the site of trauma or to the battlefield. However, both perfluorocarbons and Hb-based O_2 carriers are cleared from plasma within 24 h.

Hematopoietic progenitor cells (stem cells) from autologous or allogenic donors can be transfused as a way of reconstituting hematopoietic function (particularly immune function) in patients undergoing myeloablative or myelotoxic therapy (see p. 1132).

Technique of Transfusion

CAUTION: *Before transfusion is started, the patient's wristband, blood unit label, and compatibility test report must be checked at the bedside to ensure that the blood component is the one intended for the recipient.*

Use of an 18-gauge (or larger) needle prevents mechanical damage to and hemolysis of RBCs. A standard filter should always be used for infusion of any blood component. Only 0.9% saline IV should be allowed into the blood bag or in the same tubing with blood. Hypotonic solutions lyse RBCs, and the Ca in Ringer's lactate can cause clotting.

Transfusion of 1 unit of blood or blood component should be completed by 4 h; longer duration increases the risk of bacterial growth. If transfusion must be given slowly because of heart failure or hypervolemia, units may be divided into smaller aliquots in the blood bank. For children, 1 unit of blood can be provided in small sterile aliquots used over several days, thereby minimizing exposure to multiple donors.

Close observation is important, particularly during the first 15 min, and includes recording temperature, BP, pulse, and respiratory rate. Periodic observation continues throughout and after the transfusion, during which fluid status is assessed. The patient is kept covered and warm to prevent chills, which may be interpreted as a transfusion reaction. Elective transfusions at night are discouraged.

Complications of Transfusion

The most common complications of transfusion are febrile nonhemolytic and chill-rigor reactions. The most serious complications are transfusion-related acute lung injury and acute hemolytic reaction due to ABO incompatible transfusion, which have very high mortality rates.

Early recognition of symptoms suggestive of a transfusion reaction and prompt reporting to the blood bank are essential. The most common symptoms are chills, rigors, fever, dyspnea, light-headedness,

urticaria, itching, and flank pain. If any of these symptoms (other than localized urticaria and itching) occur, the transfusion should be stopped immediately and the IV line kept open with normal saline. The remainder of the blood product and clotted and anticoagulated samples of the patient's blood should be sent to the blood bank for investigation. NOTE: *The unit in question should not be restarted, and transfusion of any previously issued unit should not be initiated.* Further transfusion should be delayed until the cause of the reaction is known, unless the need is urgent, in which case type O Rh-negative RBCs should be used.

Hemolysis of donor or recipient RBCs (usually the former) during or after transfusion can result from ABO/Rh incompatibility, plasma antibodies, or hemolyzed or fragile RBCs (eg, by overwarming stored blood or contact with hypotonic IV solutions). Hemolysis is most common and most severe when incompatible donor RBCs are hemolyzed by antibody in the recipient's plasma. Hemolytic reactions may be acute (within 24 h) or delayed (from 1 to 14 days).

Acute hemolytic transfusion reaction (AHTR): About 20 people die yearly in the US from AHTR. AHTR usually results from recipient plasma antibodies to donor RBC antigens. ABO incompatibility is the most common cause of AHTR. Antibodies against blood group antigens other than ABO can also cause AHTR. Mislabeling the recipient's pretransfusion sample at collection or failing to match the intended recipient with the blood product immediately before transfusion is the usual cause, not laboratory error.

Hemolysis is intravascular, causing hemoglobinuria with varying degrees of acute renal failure and possibly disseminated intravascular coagulation (DIC). The severity of AHTR depends on the degree of incompatibility, the amount of blood given, the rate of administration, and the integrity of the kidneys, liver, and heart. An acute phase usually develops within 1 h of initiation of transfusion, but it may occur later during the transfusion or immediately afterward. Onset is usually abrupt. The patient may complain of discomfort and anxiety. Dyspnea, fever, chills, facial flushing, and severe pain may occur, especially in the lumbar area. Shock may develop, causing a rapid, feeble pulse; cold, clammy skin; low BP; and nausea and vomiting. Jaundice may follow acute hemolysis.

If AHTR occurs while the patient is under general anesthesia, the only symptom may be hypotension, uncontrollable bleeding from incision sites and mucous membranes caused by an associated DIC, or dark urine that reflects hemoglobinuria.

If AHTR is suspected, one of the first steps is to recheck the sample and patient identifications. Diagnosis is confirmed by measuring urinary Hb, serum LDH, bilirubin, and haptoglobin. Intravascular hemolysis produces free Hb in the plasma and urine; haptoglobin levels are very low. Hyperbilirubinemia may follow.

After the acute phase, the degree of acute renal failure determines the prognosis. Diuresis and a decreasing BUN usually portend recovery. Permanent renal insufficiency is unusual. Prolonged oliguria and shock are poor prognostic signs.

If AHTR is suspected, the transfusion should be stopped and supportive treatment begun. The goal of initial therapy is to achieve and maintain adequate BP and renal blood flow with IV 0.9% saline and furosemide. IV saline is given to maintain urine output of 100 mL/h for 24 h. The initial furosemide dose is 40 to 80 mg (1 to 2 mg/kg in children), with later doses adjusted to maintain urinary flow > 100 mL/h during the first day.

Antihypertensive drugs must be administered with caution. Pressor drugs that decrease renal blood flow (eg, epinephrine, norepinephrine, high-dose dopamine) are contraindicated. If a pressor drug is necessary, dopamine 2 to 5 µg/kg/min is usually administered.

A nephrologist should be consulted as early as possible, particularly if no diuretic response occurs within about 2 to 3 h after initiating therapy, which may indicate acute tubular necrosis. Further fluid and diuretic therapy may be contraindicated, and early dialysis may be helpful.

Delayed hemolytic transfusion reaction: Occasionally, a patient who has been sensitized to an RBC antigen has very low antibody levels and negative pretransfusion tests. After transfusion with RBCs bearing this antigen, a primary or anamnestic response may result (usually in 1 to 4 wk) and cause a

delayed hemolytic transfusion reaction. Delayed hemolytic transfusion reaction usually does not manifest as dramatically as AHTR. Patients may be asymptomatic or have a slight fever. Rarely, severe symptoms occur. Usually, only destruction of the transfused RBCs (with the antigen) occurs, resulting in a falling Hct and a slight rise in LDH and bilirubin. Because delayed hemolytic transfusion reaction is usually mild and self-limited, it is often unidentified, and the clinical clue may be an unexplained drop in Hb to the pretransfusion level occurring 1 to 2 wk posttransfusion. Severe reactions are treated similarly to acute reactions.

Febrile nonhemolytic transfusion reaction: Febrile reaction may occur without hemolysis. Antibodies directed against WBC HLA from otherwise compatible donor blood are one possible cause. This cause is most common in multitransfused or multiparous patients. Cytokines released from WBCs during storage, particularly in platelet concentrates, are another possible cause.

Clinically, febrile reactions consist of a temperature increase of ≥ 1° C, chills, and sometimes headache and back pain. Simultaneous symptoms of allergic reaction are common. Because fever and chills also herald a severe hemolytic transfusion reaction, all febrile reactions must be investigated as for AHTR, as with any transfusion reaction.

Most febrile reactions are treated successfully with acetaminophen and, if necessary, diphenhydramine (see p. 1042). Patients should also be treated (eg, with acetaminophen) before future transfusions. If a recipient has experienced more than one febrile reaction, special leukoreduction filters are used during future transfusions; most hospitals use prestorage, leukoreduced blood components.

Allergic reactions: Allergic reactions to an unknown component in donor blood are common, usually due to allergens in donor plasma or, less often, to antibodies from an allergic donor. These reactions are usually mild, with urticaria, edema, occasional dizziness, and headache during or immediately after the transfusion. Simultaneous fever is common. Less frequently, dyspnea, wheezing, and incontinence may occur, indicating a generalized spasm of smooth muscle. Rarely, anaphylaxis occurs, particularly in IgA-deficient recipients.

In a patient with a history of allergies or an allergic transfusion reaction, an antihistamine may be given prophylactically just before or at the beginning of the transfusion (eg, diphenhydramine 50 mg po or IV). NOTE: *Drugs must never be mixed with the blood.* If an allergic reaction occurs, the transfusion is stopped. An antihistamine (eg, diphenhydramine 50 mg IV) usually controls mild urticaria and itching, and transfusion may be resumed. However, a moderate allergic reaction (generalized urticaria or mild bronchospasm) requires hydrocortisone (100 to 200 mg IV), and a severe anaphylactic reaction requires additional treatment with epinephrine 0.5 mL of 1:1000 solution sc and 0.9% saline IV (see p. 1121) along with investigation by the blood bank. Further transfusion should not occur until the investigation is completed. Patients with severe IgA deficiency require transfusion of washed RBCs, washed platelets, and plasma from an IgA-deficient donor.

Volume overload: The high osmotic load of blood products draws volume into the intravascular space over the course of hours, which can cause volume overload in susceptible patients (eg, those with cardiac or renal insufficiency). RBCs should be infused slowly. The patient should be observed and, if signs of heart failure (eg, dyspnea, crackles) occur, the transfusion should be stopped and treatment for heart failure begun.

Typical treatment is with a diuretic such as furosemide 20 to 40 mg IV. Occasionally, patients requiring a higher volume of plasma infusion to reverse a warfarin overdose may be given a low dose of furosemide simultaneously; however, prothrombin complex concentrate (PCC) should be the first choice for such patients. Patients at high risk of volume overload (eg, those with heart failure or severe renal insufficiency) are treated prophylactically with a diuretic (eg, furosemide 20 to 40 mg IV).

Acute lung injury: Transfusion-related acute lung injury is an infrequent complication caused by anti-HLA and/or antigranulocyte antibodies in donor plasma that agglutinate and degranulate recipient granulocytes within the lung. Acute respiratory symptoms develop, and chest x-ray has a characteristic pattern of noncardiogenic pulmonary edema. This complication is the 2nd most common cause of transfusion-related death. Incidence is one in 5,000 to one in 10,000, but many cases are mild. Mild to

moderate transfusion-related acute lung injury probably is commonly missed. General supportive therapy typically leads to recovery without long-lasting sequelae. Diuretics should be avoided. Cases should be reported.

Altered oxygen affinity: Blood stored for > 7 days has decreased RBC 2,3-diphosphoglycerate (DPG), and the 2,3-DPG is absent after > 10 days. This absence results in an increased affinity for O_2 and slower O_2 release to the tissues. There is little evidence that 2,3-DPG deficiency is clinically significant except in exchange transfusions in infants, in sickle cell patients with acute chest syndrome and stroke, and in some patients with severe heart failure. After transfusion of RBCs, 2,3-DPG regenerates within 12 to 24 h.

Graft-vs-host disease (GVHD): Transfusion-associated GVHD (see p. 1131) is usually caused by transfusion of products containing immunocompetent lymphocytes to an immunocompromised host. The donor lymphocytes attack host tissues. GVHD can occur occasionally in immunocompetent patients if they receive blood from a donor (usually a close relative) who is homozygous for an HLA haplotype for which they are heterozygous. Symptoms and signs include fever, rash (centrifugally spreading rash becoming erythroderma with bullae), vomiting, watery and bloody diarrhea, lymphadenopathy, and pancytopenia due to bone marrow aplasia. Jaundice and elevated liver enzymes are also common. GVHD occurs 4 to 30 days after transfusion and is diagnosed based on clinical suspicion and skin and bone marrow biopsies. GVHD has > 90% mortality because no specific treatment is available.

Prevention of GVHD is with irradiation (to damage DNA of the donor lymphocytes) of all transfused blood products. It is done if the recipient is immunocompromised (eg, patients with congenital immune deficiency syndromes, hematologic cancers, or hematopoietic stem cell transplants; neonates), if donor blood is obtained from a 1st-degree relative, or when HLA-matched components, excluding stem cells, are transfused. Treatment with corticosteroids and other immunosuppressants, including those used for solid organ transplantation, is not an indication for blood irradiation.

Complications of massive transfusion: Massive transfusion is transfusion of a volume of blood greater than or equal to one blood volume in 24 h (eg, 10 units in a 70-kg adult). When a patient receives stored blood in such large volume, the patient's own blood may be, in effect, "washed out." In circumstances uncomplicated by prolonged hypotension or DIC, dilutional thrombocytopenia is the most likely complication. Platelets in stored whole blood are not functional. Clotting factors (except factor VIII) usually remain sufficient. Microvascular bleeding (abnormal oozing and continued bleeding from raw and cut surfaces) may result. Five to 8 units (1 unit/10 kg) of platelet concentrates are usually enough to correct such bleeding in an adult. Fresh frozen plasma and cryoprecipitate may be needed.

Hypothermia due to rapid transfusion of large amounts of cold blood can cause arrhythmias or cardiac arrest. Hypothermia is avoided by using an IV set with a heat-exchange device that gently warms blood. Other means of warming blood (eg, microwave ovens) are contraindicated because of potential RBC damage and hemolysis.

Citrate and K toxicities generally are not of concern even in massive transfusion; however, toxicities of both may be amplified in the presence of hypothermia. Patients with liver failure may have difficulty metabolizing citrate. Hypocalcemia can result but rarely necessitates treatment (which is 10 mL of a 10% solution of Ca gluconate IV diluted in 100 mL D_5W, given over 10 min). Patients with renal failure may have elevated K if transfused with blood stored for > 1 wk (K accumulation is usually insignificant in blood stored for < 1 wk). Mechanical hemolysis during transfusion may increase K. Hypokalemia may occur about 24 h after transfusion of older RBCs (> 3 wk), which take up K.

Infectious complications: Bacterial contamination of packed RBCs occurs rarely, possibly due to inadequate aseptic technique during collection or to transient asymptomatic donor bacteremia. Refrigeration of RBCs usually limits bacterial growth except for cryophilic organisms such as *Yersinia* sp, which may produce dangerous levels of endotoxin. All RBC units are inspected before issue for bacterial growth, which is indicated by a color change. Because platelet concentrates are stored at room temperature, they have greater potential for bacterial growth and endotoxin production if contaminated. To minimize growth, storage is limited to 5 days. The risk of bacterial contamination of platelets is 1:2500.

Therefore, platelets are routinely tested for bacteria.

Rarely, syphilis is transmitted in fresh blood or platelets. Storing blood for ≥ 96 h at 4 to 10° C kills the spirochete. Although federal regulations require a serologic test for syphilis on donor blood, infective donors are seronegative early in the disease. Recipients of infected units may develop the characteristic secondary rash.

Hepatitis may occur after transfusion of any blood product. The risk has been reduced by viral inactivation through heat treatment of serum albumin and plasma proteins and by the use of recombinant factor concentrates. Tests for hepatitis are required for all donor blood (see Table 121-2). The estimated risk of hepatitis B is 1:200,000; of hepatitis C, 1:2.6 million. Because its transient viremic phase and concomitant clinical illness likely preclude blood donation, hepatitis A (infectious hepatitis) is not a significant cause of transfusion-associated hepatitis.

HIV infection in the US is almost entirely HIV-1, although HIV-2 is also of concern. Testing for antibodies to both strains is required. Nucleic acid testing for HIV-1 antigen and HIV-1 p24 antigen testing are also required. Additionally, blood donors are asked about behaviors that may put them at high risk of HIV infection. HIV-0 has not been identified among blood donors. The estimated risk of HIV transmission due to transfusion is 1:2.6 million.

Cytomegalovirus (CMV) can be transmitted by WBCs in transfused blood. It is not transmitted through fresh frozen plasma. Because CMV does not cause disease in immunocompetent recipients, routine antibody testing of donor blood is not required. However, CMV may cause serious or fatal disease in immunocompromised patients, who should probably receive CMV-negative blood products that have been provided by CMV antibody-negative donors or by blood depleted of WBCs by filtration.

Human T-cell lymphotropic virus 1 (HTLV-1), which can cause adult T-cell lymphoma/leukemia, HTLV-1-associated myelopathy, and tropical spastic paraparesis, causes posttransfusion seroconversion in some recipients. All donor blood is tested for HTLV-1 and HTLV-2 antibodies. The estimated risk of false-negative results on testing of donor blood is 1:641,000.

Creutzfeldt-Jakob disease has never been reported to be transmitted by transfusion, but current practice precludes donation from a person who has received human-derived growth hormone or a dura mater transplant or who has a family member with Creutzfeldt-Jakob disease. New variant Creutzfeldt-Jakob disease (mad cow disease) has not been transmitted by blood transfusion. However, donors who have spent significant time in the United Kingdom and some other parts of Europe may be permanently deferred from donation (see Table 121-1).

Malaria is transmitted easily through infected RBCs. Many donors are unaware that they have malaria, which may be latent and transmissible for 10 to 15 yr. Storage does not render blood safe. Prospective donors must be asked about malaria or whether they have been in a region where it is prevalent. Donors who have had a diagnosis of malaria or who are immigrants, refugees, or citizens from countries in which malaria is considered endemic are deferred for 3 yr; travelers to endemic countries are deferred for 1 yr.

Babesiosis has rarely been transmitted by transfusion.

Therapeutic Apheresis

Therapeutic apheresis includes plasma exchange and cytapheresis, which are generally tolerated by healthy donors. However, many minor and a few major risks exist. Insertion of the large IV catheters necessary for apheresis can cause complications (eg, bleeding, infection, pneumothorax). Citrate anticoagulant may decrease serum ionized Ca. Replacement of plasma with a noncolloidal solution (eg, saline) shifts fluid from the intravascular space. Colloidal replacement solutions do not replace IgG and coagulation factors.

Most complications can be managed with close attention to the patient and manipulation of the procedure, but some severe reactions and a few deaths have occurred.

Plasma exchange: Therapeutic plasma exchange removes plasma components from blood. A blood cell separator extracts the patient's plasma and returns RBCs and platelets in plasma or a plasma-replacing fluid; for this purpose, 5% albumin is preferred to fresh frozen plasma (except for patients with thrombotic thrombocytopenic purpura) because it causes fewer reactions and transmits no infections. Therapeutic plasma exchange resembles dialysis but, in addition, can remove protein-bound toxic substances. A one-volume exchange removes about 66% of such components.

To be of benefit, plasma exchange should be used for diseases in which the plasma contains a known pathogenic substance, and plasma exchange should remove this substance more rapidly than the body produces it. For example, in rapidly progressive autoimmune disorders, plasma exchange may be used to remove existing harmful plasma components (eg, cryoglobulins, antiglomerular basement membrane antibodies) while immunosuppressive or cytotoxic drugs suppress their future production.

There are numerous indications (see Table 121-3). The frequency of plasma exchange, the volume to be removed, the replacement fluid, and other variables are individualized.

[**Table 121-3.** Indications for Plasma Exchange According to the American Society for Apheresis]

Low density lipoprotein cholesterol can be removed by plasma exchange with a recently implemented filtration method. Complications of plasma exchange are similar to those of therapeutic cytapheresis.

Cytapheresis: Therapeutic cytapheresis removes cellular components from blood, returning plasma. It is most often used to remove defective RBCs and substitute normal ones in patients with sickle cell anemia who have the following conditions: acute chest syndrome, stroke, pregnancy, or frequent, severe sickle cell crises. Cytapheresis achieves Hb S levels of < 30% without the risk of increased viscosity that can occur because of increased Hct with simple transfusion.

Therapeutic cytapheresis may also be used to reduce severe thrombocytosis or leukocytosis (cytoreduction) in acute or chronic leukemia when there is risk of hemorrhage, thrombosis, or pulmonary or cerebral complications of extreme leukocytosis (leukostasis). Cytapheresis is effective in thrombocytosis because platelets are not replaced as rapidly as WBCs. One or 2 procedures may reduce platelet counts to safe levels. Therapeutic WBC removal (leukapheresis) can remove kilograms of buffy coat in a few procedures, and it often relieves leukostasis and splenomegaly. However, the reduction in WBC count itself may be mild and only temporary.

Other uses of cytapheresis include collection of peripheral blood stem cells for autologous or allogeneic bone marrow reconstitution (an alternative to bone marrow transplantation) and collection of lymphocytes for use in immune modulation cancer therapy (adoptive immunotherapy).

Chapter 122. Overview of Cancer

Introduction

Cancer is an unregulated proliferation of cells due to loss of normal controls, resulting in unregulated growth, lack of differentiation, local tissue invasion, and, often, metastasis. Cancer can develop in any tissue or organ at any age. There is often evidence of an immune response to tumors, but the role of the immune system in preventing and treating cancer is still uncertain.

Many cancers are curable if detected at an early stage, and long-term remission is often possible in later stages. However, cure is not always possible and is not attempted in some advanced cases in which palliative care provides better quality of life than aggressive treatment, particularly in the elderly or in patients with underlying comorbid disorders.

Cellular and Molecular Basis of Cancer

Cellular Kinetics

Generation time is the time required for a quiescent cell to complete a cycle in cell division (see Fig. 122-1) and give rise to 2 daughter cells. Malignant cells usually have a shorter generation time than nonmalignant cells from the same tissue, and there usually are a smaller percentage of cells in G_0 (resting phase). Initial exponential tumor growth is followed by a plateau phase when cell death nearly equals the rate of formation of daughter cells. The slowing in growth rate is likely related to exhaustion of the supply of nutrients and O_2 for the rapidly expanding

[**Fig. 122-1.** The cell cycle.]

tumor. Small tumors have a greater percentage of actively dividing cells than do large tumors.

Cellular kinetics of particular tumors is an important consideration in the design of antineoplastic drug regimens and may influence the dosing schedules and timing intervals of treatment. Many antineoplastic drugs are effective only if cells are actively dividing, and some drugs work only during a specific phase of the cell cycle and thus require prolonged administration to catch dividing cells during the phase of maximal sensitivity.

Tumor Growth and Metastasis

As a tumor grows, nutrients are provided by direct diffusion from the circulation. Local growth is facilitated by enzymes (eg, proteases) that destroy adjacent tissues. As tumor volume increases, tumor angiogenesis factors are produced to promote formation of the vascular supply required for further tumor growth.

Almost from inception, a tumor may shed cells into the circulation. From animal models, it is estimated that a 1-cm tumor sheds > 1 million cells/24 h into the venous circulation. Although most circulating tumor cells die as a result of intravascular trauma, an occasional cell may adhere to the vascular endothelium and penetrate into surrounding tissues, generating independent tumors (metastases) at distant sites. Metastatic tumors grow in much the same manner as primary tumors and may subsequently give rise to other metastases.

Experiments suggest that through random mutation, a subset of cells in the primary tumor may acquire the ability to invade and migrate to distant sites, resulting in metastasis.

Molecular Abnormalities

Genetic mutations are responsible for the generation of cancer cells. These mutations alter the quantity or function of protein products that regulate cell growth and division and DNA repair. Two major categories of mutated genes are oncogenes and tumor suppressor genes.

Oncogenes: These are abnormal forms of normal genes (proto-oncogenes) that regulate various aspects of cell growth. Mutation of these genes may result in direct and continuous stimulation of the pathways (eg, intracellular signal transduction pathways, transcription factors, secreted growth factors) that control cellular growth and division, DNA repair, angiogenesis, and other physiologic processes.

There are > 100 known oncogenes that may contribute to human neoplastic transformation. For example, the ras gene encodes the Ras protein, which regulates cell division. Mutations may result in the inappropriate activation of the Ras protein, leading to uncontrolled cell growth and division. In fact, the Ras protein is abnormal in about 25% of human cancers. Other oncogenes have been implicated in specific cancers. These include

• *Her2/neu* (breast cancer)

• *BCR-ABL* (chronic myelocytic leukemia, B-cell acute lymphocytic leukemia)

• C-*myc* (Burkett's lymphoma)

• N-*myc* (small cell lung cancer, neuroblastoma)

Specific oncogenes may have important implications for diagnosis, therapy, and prognosis (see individual discussions under the specific cancer type).

Oncogenes typically result from acquired somatic cell mutations secondary to point mutations (eg, from chemical carcinogens), gene amplification (eg, an increase in the number of copies of a normal gene), or translocations. Occasionally, mutation of genes results in inheritance of a cancer predisposition, as in the inheritance of *BRCA1* or *BRCA2* in families with a high incidence of breast or ovarian cancer.

Tumor suppressor genes: Genes such as the *p53* gene play a role in normal cell division and DNA repair and are critical for detecting inappropriate growth signals in cells. If these genes, as a result of inherited or acquired mutations, become unable to function, genetic mutations in other genes can proceed unchecked, leading to neoplastic transformation.

As with most genes, 2 alleles are present that encode for each tumor suppressor gene. A defective copy of one gene may be inherited, leaving only one functional allele for the individual tumor suppressor gene. If a mutation is acquired in the other allele, the normal protective mechanisms of the tumor suppressor gene are lost, and dysfunction of other protein products or DNA damage may escape unregulated, leading to cancer. For example, the retinoblastoma (*RB*) gene encodes for the protein Rb, which regulates the cell cycle by stopping DNA replication. Mutations in the *RB* gene family occur in many human cancers, allowing affected cells to divide continuously.

Another important regulatory protein, p53, prevents replication of damaged DNA in normal cells and promotes cell death (apoptosis) in cells with abnormal DNA. Inactive or altered p53 allows cells with abnormal DNA to survive and divide. Mutations are passed to daughter cells, conferring a high probability of neoplastic transformation. The *p53* gene is defective in many human cancers. As with oncogenes, mutation of tumor suppressor genes such as *p53* or *RB* in germ cell lines may result in vertical transmission and a higher incidence of cancer in offspring.

Chromosomal abnormalities: Gross chromosomal abnormalities (see p. 2997) can occur through deletion, translocation, or duplication. If these alterations activate or inactivate genes that result in a proliferative advantage over normal cells, then a tumor may develop. Chromosomal abnormalities occur in certain human cancers (see Table 122-1). In some congenital diseases (Bloom syndrome, Fanconi's anemia, Down syndrome), DNA repair processes are defective and chromosomes break easily, putting children at high risk of developing acute leukemia and lymphomas.

Other influences: Most cancers likely involve several of the mechanisms described above that lead to neoplastic conversion. For example, the development of tumor in familial polyposis takes place through a

sequence of genetic events: epithelium hyperproliferation (loss of a suppressor gene on chromosome 5), early adenoma (change in DNA methylation), intermediate adenoma (overactivity of the *ras* oncogene), late adenoma (loss of a suppressor gene on chromosome 18), and finally, cancer (loss of a gene on chromosome 17). Further genetic changes may be required for metastasis.

Telomeres are nucleoprotein complexes that cap the ends of chromosomes and maintain their integrity. In normal tissue, telomere shortening (which occurs with aging) results in a finite limit in cell division. The enzyme telomerase provides for telomere synthesis and maintenance; thus telomerase may potentially allow for cellular immortality. Activation of telomerase in tumors allows continuous proliferation of tumors.

Environmental Factors

Infections: Viruses contribute to the pathogenesis of human cancers (see Table 122-2). Pathogenesis may occur through the integration of viral genetic elements into the host DNA. These new genes are expressed by the host; they may affect cell growth or division or disrupt normal host genes required for control of cell growth and division. Alternatively, viral infection may result in immune dysfunction, leading to decreased immune surveillance for early tumors.

Bacteria may also cause cancer. *Helicobacter pylori* infection increases the risk of

[**Table 122-1.** Human Cancers Associated with Chromosomal Abnormalities]

[**Table 122-2.** Cancer-Associated Viruses]

several kinds of cancer (gastric adenocarcinoma, gastric lymphoma, mucosa-associated lymphoid tissue [MALT] lymphoma).

Parasites of some types can lead to cancer. *Schistosoma haematobium* causes chronic inflammation and fibrosis of the bladder, which may lead to cancer. *Opisthorchis sinensis* has been linked to carcinoma of the pancreas and bile ducts.

Radiation: Ultraviolet radiation may induce skin cancer (eg, basal and squamous cell carcinoma, melanoma) by damaging DNA. This DNA damage consists of formation of thymidine dimers, which may escape repair because of inherent defects in DNA repair (eg, xeroderma pigmentosum) or through rare, random events.

Ionizing radiation is also carcinogenic. For example, survivors of the atomic bomb explosions in Hiroshima and Nagasaki have a higher-than-expected incidence of leukemia and other cancers. Similarly, the previous use of x-rays to treat nonmalignant disease (acne, thymic or adenoid enlargement, and ankylosing spondylitis) resulted in higher rates of acute and chronic leukemias, Hodgkin and non-Hodgkin lymphomas, multiple myeloma, aplastic anemia terminating in acute nonlymphocytic leukemia, myelofibrosis, melanoma, and thyroid cancer. Use of x-rays in diagnostic imaging studies is thought to increase risk of cancer (see p. 3402). Industrial exposure (eg, to uranium by mine workers) is linked to development of lung cancer after a 15- to 20-yr latency. Long-term exposure to occupational irradiation or to internally deposited thorium dioxide predisposes people to angiosarcomas and acute nonlymphocytic leukemia.

Exposure to the radioactive gas radon, which is released from soil, increases the risk of lung cancer. Normally, radon disperses rapidly into the atmosphere and causes no harm. However, when a building is placed on soil with high radon content, radon can accumulate within the building, sometimes producing sufficiently high levels in the air to cause harm. In exposed people who also smoke, the risk of lung cancer is further increased.

Drugs and chemicals: Estrogens in oral contraceptives may slightly increase the risk of breast cancer, but this risk decreases over time. Estrogen and progestin used for hormone replacement therapy also increase the risk of breast cancer. Diethylstilbestrol (DES) increases the risk of breast cancer in women who took the drug and increases the risk of vaginal carcinoma in daughters of these women who were exposed before birth. Long-term use of anabolic steroids may increase the risk of liver cancer. Treatment

of cancer with chemotherapy drugs and with radiation therapy increases the risk of developing a second cancer.

Chemical carcinogens can induce gene mutations and result in uncontrolled growth and tumor formation (see Table 122-3). Other substances, called co-carcinogens, have little or no inherent carcinogenic potency but enhance the carcinogenic effect of another agent when exposed simultaneously.

Dietary substances: Certain substances consumed in the diet can increase the risk of cancer. For instance, a diet high in fat has been linked to an increased risk of colon, breast, and possibly prostate cancer. People who drink large amounts of alcohol are at much higher risk of developing esophageal cancer. A diet high in smoked and pickled foods or in barbecued meats increases the risk of developing stomach cancer. People who are overweight or obese have a higher risk of cancer of the breast, endometrium, colon, kidneys, and esophagus.

Physical factors: Chronic skin irritation leads to chronic dermatitis and, in rare cases, to squamous cell carcinoma. This occurrence is presumably due to random mutations that occur more frequently because of the increased cell turnover.

Immunologic Disorders

Immune system dysfunction as a result of inherited genetic mutation, acquired disorders, aging, or immunosuppressants interferes with

[**Table 122-3.** Common Chemical Carcinogens]

normal immune surveillance of early tumors and results in higher rates of cancer. Known cancer-associated immune disorders include

- Ataxia-telangiectasia (acute lymphocytic leukemia [ALL], brain tumors, gastric cancer)
- Wiskott-Aldrich syndrome (lymphoma, ALL)
- X-linked agammaglobulinemia (lymphoma, ALL)
- Immune deficiency secondary to immunosuppressants or HIV infection (large cell lymphoma, Kaposi's sarcoma)
- Rheumatologic conditions, such as SLE, RA, and Sjogren's syndrome (B-type lymphoma)
- General immune disorders (lymphoreticular neoplasia)

Cancer Diagnosis

A diagnosis of cancer may be suspected based on history and physical examination but requires confirmation by tumor biopsy and histopathologic examination.

A complete history and physical examination may reveal unexpected clues to early cancer.

History

Physicians must be aware of predisposing factors and must specifically ask about familial cancer, environmental exposure (including smoking history), and prior or present illnesses (eg, autoimmune disorders, previous immunosuppressive therapy, hepatitis B or hepatitis C, HIV infection, abnormal Papanicolaou test, human papillomavirus infection). Symptoms suggesting occult cancer can include

- Fatigue

- Weight loss
- Fevers
- Night sweats
- Cough
- Hemoptysis
- Hematemesis
- Hematochezia
- Change in bowel habits
- Persistent pain

Physical examination

Particular attention should be paid to skin, lymph nodes, lungs, breasts, abdomen, and testes. Prostate, rectal, and vaginal examinations are also important. Findings help direct further testing, including x-rays and biopsies.

Testing

Tests include imaging tests, serum tumor markers, and biopsy.

Imaging tests often include plain x-rays, ultrasonography, CT, and MRI. These tests assist in identifying abnormalities, determining qualities of a mass (solid or cystic), providing dimensions, and establishing relationship to surrounding structures, which may be important if surgery or biopsy is being considered.

Serum tumor markers may offer corroborating evidence in patients with findings suggestive of a specific cancer (see p. 1058). With some exceptions (eg, prostate-specific antigen [PSA]), these markers do not have enough sensitivity and specificity to be used for screening. They are the most useful in detecting early relapse and monitoring response to therapy. Useful examples include

- α-Fetoprotein (hepatocellular carcinoma, testicular carcinoma)
- Carcinoembryonic antigen (colon cancer)
- β-human chorionic gonadotropin (choriocarcinoma, testicular carcinoma)
- Serum immunoglobulins (multiple myeloma)
- DNA probes (eg, *bcr* probe to identify a chromosome 22 alteration in chronic myelogenous leukemia)
- CA 125 (ovarian cancer)
- CA 27-29 (breast cancer)
- PSA (prostate cancer)

Biopsy to confirm the diagnosis and tissue of origin is almost always required when cancer is suspected or detected. The choice of biopsy site is usually determined by ease of access and degree of invasiveness. If lymphadenopathy is present, fine-needle or core biopsy may yield the tumor type; if nondiagnostic, open biopsy is done. Other biopsy routes include bronchoscopy for easily accessible mediastinal or central pulmonary tumors, percutaneous liver biopsy if liver lesions are present, and CT- or

ultrasound-guided biopsy. If these procedures are not suitable, open biopsy may be necessary.

Grading is a histologic measure of tumor aggressiveness and provides important prognostic information. It is determined by examining the biopsy specimen. Grade is based on the morphologic appearance of tumor cells, including the appearance of the nuclei, cytoplasm, and nucleoli; frequency of mitoses; and amount of necrosis. For many cancers, grading scales have been developed.

Molecular tests such as chromosomal analogs, fluorescent in situ hybridization (FISH), PCR, and cell surface antigens (eg, in lymphomas, leukemias) delineate the origin of metastatic cancers originating from an unknown primary cancer or assist in recognizing chemotherapy resistance (eg, in acute myelogenous leukemia).

Staging

Once a histologic diagnosis is made, staging (ie, determination of the extent of disease) helps determine treatment decisions and prognosis. Clinical staging uses data from the history, physical examination, imaging tests, laboratory tests, and biopsy of bone marrow, lymph nodes, or other sites of suspected disease. For staging of specific neoplasms, see details in the organ-relevant chapter.

Imaging tests: Imaging tests, especially CT and MRI, can detect metastases to brain, lungs, or abdominal viscera, including the adrenal glands, retroperitoneal lymph nodes, liver, and spleen. MRI (with gadolinium contrast) is the procedure of choice for recognition and evaluation of brain tumors, both primary and metastatic. PET scanning is increasingly being used to determine the metabolic activity of a suspect lymph node or mass. Integrated PET-CT can be valuable, especially in lung, head and neck, and breast cancer and in lymphoma.

Ultrasonography can be used to study orbital, thyroid, cardiac, pericardial, hepatic, pancreatic, renal, and retroperitoneal areas. It may guide percutaneous biopsies and differentiate renal cell carcinoma from a benign renal cyst.

Nuclear scans can identify several types of metastases. Bone scans identify abnormal bone growth (ie, osteoblastic activity) before it is visible on plain x-ray. Thus, this technique is useless in neoplasms that are purely lytic (eg, multiple myeloma); routine bone x-rays are the study of choice in such diseases.

Laboratory tests: Serum chemistries and enzymes may help staging. Elevated liver enzyme (alkaline phosphatase, LDH, ALT) levels suggest the presence of liver metastases. Elevated alkaline phosphatase and serum Ca may be the first evidence of bone metastases. Elevated BUN or creatinine levels may indicate an obstructive uropathy secondary to a pelvic mass, intrarenal obstruction from tubular precipitation of myeloma protein, or uric acid nephropathy from lymphoma or other cancers. Elevated uric acid levels often occur in myeloproliferative and lymphoproliferative disorders.

Invasive tests: Mediastinoscopy (see p. 1863) is especially valuable in the staging of non-small cell lung cancer. When mediastinal lymph node involvement is found, patients do not usually benefit from thoracotomy and lung resection but may benefit from chemoradiation and subsequent tumor resection.

Bone marrow aspiration and biopsy are especially useful in detecting metastases from malignant lymphoma and small cell lung cancer, and their role in breast and prostate cancer staging is expanding. Bone marrow biopsy is positive at diagnosis in 50 to 70% of patients with malignant lymphoma (low and intermediate grade) and in 15 to 18% of patients with small cell lung cancer. Bone marrow biopsy should be done in patients with hematologic abnormalities (ie, anemia, thrombocytopenia, pancytopenia) that cannot be explained by other mechanisms.

Biopsy of regional lymph nodes is part of the evaluation of most tumors, such as breast, lung, or colon cancers.

Cancer Screening

Cancer can sometimes be detected in asymptomatic patients via regular physical examinations and

screening tests.

Physical examinations for cancers of the thyroid, oral cavity, skin, lymph nodes, testes, prostate, and ovaries should also be done during routine medical care.

Screening tests are done in asymptomatic patients at risk. The rationale is that early diagnosis may decrease cancer mortality by detecting cancer at an early and curable stage. Early detection may allow for less radical therapy and reduce costs. Risks, however, include false-positive results, which necessitate confirmatory tests (eg, biopsy, endoscopy) that can lead to anxiety, significant morbidity, and significant costs; and false-negative results, which may give a mistaken sense of security, causing patients to ignore subsequent symptoms.

Screening for cancer should be done in the following circumstances:

- When distinct high-risk groups can be identified (eg, people with certain infections, exposures, or behaviors)
- When the disorder has an asymptomatic period during which treatment would alter outcome
- When the morbidity of the disorder is significant
- When an intervention is available that is acceptable and effective at changing the natural history of the disorder

The screening tests themselves should satisfy the following criteria:

- Cost and convenience are reasonable.
- Results are reliable and reproducible.
- Sensitivity and specificity are adequate.
- The positive predictive value (probability that a person with a positive test result has or will develop a disorder or condition—see p. 3391) is high in the population screened, and few false-negative results occur.
- The test or procedure is acceptable to patients.

Recommended screening schedules are constantly evolving based on ongoing studies (see Table 122-4).

Clinical Sequelae of Cancer

Cancer may lead to pain, weight loss, neuropathy, nausea, fatigue, seizures, or obstruction of visceral organs. Death typically occurs as a result of failure of one or more organ systems.

Pain in patients with metastatic cancer frequently results from bone metastases, nerve or plexus involvement, or pressure exerted by a tumor mass or effusion. Aggressive pain management is essential in the treatment of cancer and for maintenance of quality of life (see p. 1623).

Cardiac tamponade can result from malignant pericardial effusion and often occurs precipitously. The most common causes are breast cancer, lung cancer, and lymphoma. The preceding effusion may cause ill-defined chest pain or pressure that is worse when patients are supine and better when they are sitting up (see p. 2203). Patients with tamponade may experience signs and symptoms of decreased cardiac output (eg, dizziness or syncope). On physical examination, heart signs may be muffled and a friction rub and pulsus paradoxus may be present. X-ray may show a globular cardiac silhouette. Pericardiocentesis should be done for diagnostic and therapeutic purposes, and a pleuropericardial window or pericardiectomy should be considered.

Pleural effusions should be drained if symptomatic and monitored for reaccumulation. If the effusion reaccumulates rapidly, thoracostomy tube drainage (see p. 1866) and sclerosing agents or repeated catheter drainage should be considered. Palliative surgical pleurectomy can be used for refractory effusions in advanced malignant disease.

Spinal cord compression (see p. 1810) can result from cancer spread to the vertebrae and requires immediate surgery or radiation therapy. Symptoms may include back pain, lower extremity paresthesias, and bowel and bladder

[**Table 122-4.** Screening Procedures in Average-Risk Asymptomatic People as Recommended by the American Cancer Society*]

dysfunction. Diagnosis is confirmed by CT or MRI.

Clots in the veins of the lower extremities often cause complications in cancer patients. Tumors produce procoagulants, such as tissue factors, leading to excess clot formation, particularly in after surgery. Anticoagulants may be necessary to prevent pulmonary emboli.

Metabolic and immune consequences of cancer can include hypercalcemia, hyperuricemia, increased ACTH production, antibodies that produce neurologic dysfunction, hemolytic anemia, and many other complications.

Metastatic Carcinoma of Unknown Primary Origin

A patient is considered to have carcinoma of unknown primary origin when a tumor is detected at one or more metastatic sites and routine evaluation fails to identify a primary tumor. Metastatic carcinoma of unknown primary origin constitutes up to 7% of all cancers and poses a therapeutic dilemma, because cancer treatment is typically directed at the specific primary tissue type.

The most common causative primary tumors are those of the testes, lungs, colon and rectum, and pancreas. Examination of these areas should be thorough.

Types of testing used to help specify the primary site include

• Laboratory testing

• Imaging tests

• Immunocytochemical and immunoperoxidase staining

• Tissue analysis

Laboratory tests should include a CBC, urinalysis, stool examination for occult blood, and serum chemistries (including prostate-specific antigen assays in males).

Imaging should be limited to a chest x-ray, abdominal CT, and mammography. An upper GI series and barium enema should be done if blood is present in the stool.

Increasing numbers of immunocytochemical stains can be used to test available cancerous tissue to help determine the primary tissue site. In addition, immunoperoxidase staining for immunoglobulin, gene rearrangement studies, and electron microscopy help diagnose large cell lymphoma, whereas immunoperoxidase staining for α-fetoprotein or β-human chorionic gonadotropin may suggest germ cell tumors. Tissue analysis for estrogen and progesterone receptors helps identify breast cancer, and immunoperoxidase staining for prostate-specific antigen helps identify prostate cancer.

Even if a precise histologic diagnosis cannot be made, one constellation of findings may suggest an origin. Poorly differentiated carcinomas near or at midline regions of the mediastinum or retroperitoneum

in young or middle-aged males should be considered germ cell neoplasms—even in the absence of a testicular mass. Patients with this type of carcinoma should be treated with a cisplatin-based regimen, because nearly 50% of such patients experience long disease-free intervals. For most other unknown primary cancers, the responses to this regimen and to other multidrug chemotherapy regimens are modest and of brief duration (eg, median survival < 1 yr).

Paraneoplastic Syndromes

Paraneoplastic syndromes are symptoms that occur at sites distant from a tumor or its metastasis.

Although the pathogenesis remains unclear, these symptoms may be secondary to substances secreted by the tumor or may be a result of antibodies directed against tumors that cross-react with other tissue. Symptoms may occur in any organ or physiologic system. Up to 20% of cancer patients experience paraneoplastic syndromes, but often these syndromes are unrecognized.

The most common cancers associated with paraneoplastic syndromes include

• Lung carcinoma (most common)

• Renal carcinoma

• Hepatocellular carcinoma

• Leukemias

• Lymphomas

• Breast tumors

• Ovarian tumors

• Neural cancers

• Gastric cancers

• Pancreatic cancers

Successful treatment is best obtained by controlling the underlying cancer, but some symptoms can be palliated with specific drugs (eg, cyproheptadine for carcinoid syndrome, bisphosphonates and corticosteroids for hypercalcemia).

General paraneoplastic symptoms: Patients with cancer often experience fever, night sweats, anorexia, and cachexia. These symptoms may arise from release of cytokines involved in the inflammatory or immune response or from mediators involved in tumor cell death, such as tumor necrosis factor-α. Alterations in liver function and steroidogenesis may also contribute.

Cutaneous paraneoplastic syndromes: Patients may experience many skin symptoms.

Itching is the most common cutaneous symptom experienced by patients with cancer (eg, leukemia, lymphomas) and may result from hypereosinophilia.

Flushing may also occur and is likely related to tumor-generated circulating vasoactive substances (eg, prostaglandins).

Pigmented skin lesions, or keratoses, may appear, including acanthosis nigricans (GI cancer), generalized dermic melanosis (lymphoma, melanoma, hepatocellular carcinoma), Bowen's disease (lung, GI, GU cancer), and large multiple seborrheic keratoses, ie, Leser-Trelat signs (lymphoma, GI cancer).

Secretion of melanin precursors from tumors may promote formation of these lesions.

Ichthyosis, or desquamation of the extensor surface of the extremities, may also occur.

Hypertrichosis may manifest as sudden appearance of coarse hair on the face and ears that resolves after resection or treatment of the tumor. Alternatively, alopecia may occur with certain tumor types. The mechanism by which alopecia occurs is not clear.

Necrotizing migrating erythema may occur with glucagonomas.

Subcutaneous adipose nodular necrosis may result from release of proteolytic enzymes from various pancreatic tumors.

Herpes zoster may result from reactivation of latent virus in patients with immune system depression or dysfunction.

Endocrine paraneoplastic syndromes: The endocrine system is often affected by paraneoplastic syndromes.

Cushing's syndrome (cortisol excess, leading to hyperglycemia, hypokalemia, hypertension, central obesity, moon facies) may result from ectopic production of ACTH or ACTH-like molecules, most often with small cell cancer of the lung.

Abnormalities in water and electrolyte balance, including hyponatremia, may result from production of ADH and parathyroid hormone-like hormones from small cell and non-small cell lung cancer.

Hypoglycemia may result from production of insulin-like growth factors or insulin production by pancreatic islet cell tumors or hemangiopericytomas.

Hypertension may result from abnormal epinephrine and norepinephrine secretion (pheochromocytomas) or from cortisol excess (ACTH-secreting tumors).

Other ectopically produced hormones include parathyroid hormone-related peptide (PTHRP—from squamous cell lung cancer, head and neck cancer, bladder cancer), calcitonin (from breast cancer, small cell lung cancer, and medullary thyroid carcinoma), and thyroid-stimulating hormone (from gestational choriocarcinoma). PTHRP causes hypercalcemia and its associated symptoms (polyuria, dehydration, constipation, muscle weakness); calcitonin causes a fall in the serum Ca level, with contractions and cardiac arrhythmias.

GI paraneoplastic syndromes: Watery diarrhea with subsequent dehydration and electrolyte imbalances may result from tumor-related secretion of prostaglandins or vasoactive intestinal peptide. Implicated tumors include pancreatic islet cell tumors and others. Protein-losing enteropathies may result from tumor mass inflammation, particularly with lymphomas.

Hematologic paraneoplastic syndromes: Patients with cancer may develop pure RBC aplasia, anemia of chronic disease, leukocytosis (leukemoid reaction), thrombocytosis, eosinophilia, basophilia, and disseminated intravascular coagulation. In addition, idiopathic thrombocytopenic purpura and a Coombs'-positive hemolytic anemia can complicate the course of lymphoid cancers and Hodgkin lymphoma. Erythrocytosis may occur in various cancers, especially renal cancers and hepatomas, due to ectopic production of erythropoietin or erythropoietin-like substances, and monoclonal gammopathies may sometimes be present.

Demonstrated mechanisms of hematologic abnormalities include tumor-generated substances that mimic or block normal endocrine signals for hematologic line development and generation of antibodies that cross-react with receptors or cell lines.

Neurologic paraneoplastic syndromes: Several types of peripheral neuropathy are among the neurologic paraneoplastic syndromes. Cerebellar syndromes and other central neurologic paraneoplastic

syndromes also occur.

Peripheral neuropathy is the most common neurologic paraneoplastic syndrome. It is usually a distal sensorimotor polyneuropathy that causes mild motor weakness, sensory loss, and absent distal reflexes. The syndrome is indistinguishable from that accompanying many chronic illnesses.

Subacute sensory neuropathy is a more specific but rare peripheral neuropathy. Dorsal root ganglia degeneration and progressive sensory loss with ataxia but little motor weakness develop; the disorder may be disabling. Anti-Hu, an autoantibody, is found in the serum of some patients with lung cancer. There is no treatment.

Guillain-Barre syndrome, another peripheral neuropathy, is more common in patients with Hodgkin lymphoma than in the general population.

Eaton-Lambert syndrome is an immune-mediated, myasthenia-like syndrome with weakness usually affecting the limbs and sparing ocular and bulbar muscles. It is pre-synaptic, resulting from impaired release of acetylcholine from nerve terminals. An IgG antibody is involved. The syndrome can precede, occur with, or develop after the diagnosis of cancer. It occurs most commonly in men with intrathoracic tumors (70% have small or oat cell lung carcinoma). Symptoms and signs include fatigability, weakness, pain in proximal limb muscles, peripheral paresthesias, dry mouth, erectile dysfunction, and ptosis. Deep tendon reflexes are reduced or lost. The diagnosis is confirmed by finding an incremental response to repetitive nerve stimulation: Amplitude of the compound muscle action potential increases > 200% at rates > 10 Hz. Treatment is first directed at the underlying cancer and sometimes induces remission. Guanidine (initially 125 mg po qid, gradually increased to a maximum of 35 mg/kg), which facilitates acetylcholine release, often lessens symptoms but may depress bone marrow and liver function. Corticosteroids and plasmapheresis benefit some patients.

Subacute cerebellar degeneration causes progressive bilateral leg and arm ataxia, dysarthria, and sometimes vertigo and diplopia. Neurologic signs may include dementia with or without brain stem signs, ophthalmoplegia, nystagmus, and extensor plantar signs, with prominent dysarthria and arm involvement. Cerebellar degeneration usually progresses over weeks to months, often causing profound disability. Cerebellar degeneration may precede the discovery of the cancer by weeks to years. Anti-Yo, a circulating autoantibody, is found in the serum or CSF of some patients, especially women with breast or ovarian cancer. MRI or CT may show cerebellar atrophy, especially late in the disease. Characteristic pathologic changes include widespread loss of Purkinje cells and lymphocytic cuffing of deep blood vessels. CSF occasionally has mild lymphocytic pleocytosis. Treatment is nonspecific, but some improvement may follow successful cancer therapy.

Opsoclonus (spontaneous chaotic eye movements) is a rare cerebellar syndrome that may accompany childhood neuroblastoma. It is associated with cerebellar ataxia and myoclonus of the trunk and extremities. Anti-Ri, a circulating autoantibody, may be present. The syndrome often responds to corticosteroids and treatment of the cancer.

Subacute motor neuronopathy is a rare disorder causing painless lower motor neuron weakness of upper and lower extremities, usually in patients with Hodgkin lymphoma or other lymphomas. Anterior horn cells degenerate. Spontaneous improvement usually occurs.

Subacute necrotizing myelopathy is a rare syndrome in which rapid ascending sensory and motor loss occurs in gray and white matter of the spinal cord, leading to paraplegia. MRI helps rule out epidural compression from metastatic tumor—a much more common cause of rapidly progressive spinal cord dysfunction in patients with cancer. MRI may show necrosis in the spinal cord.

Encephalitis may occur as a paraneoplastic syndrome, taking several different forms, depending on the area of the brain involved. Global encephalitis has been proposed to explain the encephalopathy that occurs most commonly in small cell lung cancer. Limbic encephalitis is characterized by anxiety and depression, leading to memory loss, agitation, confusion, hallucinations, and behavioral abnormalities. Anti-Hu antibodies, directed against RNA binding proteins, may be present in the serum and spinal fluid. MRI may disclose areas of increased contrast uptake and edema.

Renal paraneoplastic syndrome: Membranous glomerulonephritis may occur in patients with colon cancer, ovarian cancer, and lymphoma as a result of circulating immune complexes.

Rheumatologic paraneoplastic syndromes: Rheumatologic disorders mediated by autoimmune reactions can also be a manifestation of paraneoplastic syndromes.

Arthropathies (rheumatic polyarthritis, polymyalgia) or systemic sclerosis may develop in patients with hematologic cancers or with cancers of the colon, pancreas, or prostate. Systemic sclerosis or SLE may also develop in patients with lung and gynecologic cancers.

Hypertrophic osteoarthropathy is prominent with certain lung cancers and manifests as painful swelling of the joints (knees, ankles, wrists, elbows, metacarpophalangeal joints) with effusion and sometimes fingertip clubbing.

Secondary amyloidosis may occur with myeloma, lymphomas, or renal cell carcinomas.

Dermatomyositis and, to a lesser degree, **polymyositis** (see p. 299) are thought to be more common in patients with cancer, especially in those > 50 yr. Typically, proximal muscle weakness is progressive with pathologically demonstrable muscle inflammation and necrosis. A dusky, erythematous butterfly rash with a heliotrope hue may develop on the cheeks with periorbital edema. Corticosteroids may be helpful.

Chapter 123. Tumor Immunology

Introduction

Tumor recognition is a complex, challenging problem for the immune system, which must distinguish proper cellular growth and organization from neoplastic transformation. This process involves recognition of tumor antigens by effector cells and induction of immunity. The development of tumors despite the presence of antigens, the significance of immune recognition in the pathogenesis of tumors, and the potential for therapeutic augmentation of immune responses remain the subject of intense investigation.

Tumor Antigens

Many tumor cells produce antigens, which may be released in the bloodstream or remain on the cell surface. Antigens have been identified in most of the human cancers, including Burkitt's lymphoma, neuroblastoma, malignant melanoma, osteosarcoma, renal cell carcinoma, breast carcinoma, prostate cancer, lung carcinomas, and colon cancer. A key role of the immune system is detection of these antigens to permit subsequent targeting for eradication. However, despite their foreign structure, the immune response to tumor antigens varies and is often insufficient to prevent tumor growth.

Tumor-associated antigens (TAAs) are relatively restricted to tumor cells, whereas tumor-specific antigens (TSAs) are unique to tumor cells. TSAs and TAAs typically are portions of intracellular molecules expressed on the cell surface as part of the major histocompatibility complex.

Suggested mechanisms of origin for tumor antigens include

- Introduction of new genetic information from a virus (eg, human papillomavirus E6 and E7 proteins in cervical cancer)

- Alteration of oncogenes or tumor suppressor genes by carcinogens, which either generate a novel protein sequence directly or induce accumulation of proteins that are normally not expressed or are expressed at very low levels (eg, *ras, p53*)

- Abnormally high levels of proteins that normally are present at substantially lower levels (eg, prostate-specific antigens, melanoma-associated antigens) or that are expressed only during embryonic development (carcinoembryonic antigens)

- Uncovering of antigens normally buried in the cell membrane because of defective membrane homeostasis in tumor cells

- Release of antigens normally sequestered within the cell or its organelles when tumor cells die

Host Response to Tumors

The immune response to foreign antigens consists of humoral (eg, antibodies) and cellular mechanisms. Most humoral responses cannot prevent tumor growth. However, effector cells, such as T cells, macrophages, and natural killer cells, have relatively effective tumoricidal abilities. Effector cell activity is induced by cells that present tumor-specific antigens (TSAs) or tumor-associated antigens (TAAs) on their surface (these cells are called antigen-presenting cells) and is supported by cytokines (eg, interleukins, interferons—see p. 1084). Despite the activity of effector cells, host immunoreactivity may fail to control tumor occurrence and growth.

Cellular Immunity

The T cell is the primary cell responsible for direct recognition and killing of tumor cells. T cells carry out immunologic surveillance, then proliferate and destroy newly transformed tumor cells after recognizing TAAs. The T-cell response to tumors is modulated by other cells of the immune system; some cells require the presence of humoral antibodies directed against the tumor cells (antibody-dependent cellular cytotoxicity) to initiate the interactions that lead to the death of tumor cells. In contrast, suppressor T cells

inhibit the immune response against tumors.

Cytotoxic T lymphocytes (CTLs) recognize antigens on target cells and lyse these cells. These antigens may be cell surface proteins or may be intracellular proteins (eg, TAAs) that are expressed on the surface in combination with class I major histocompatibility complex (MHC) molecules. Tumor-specific CTLs have been found with neuroblastomas; malignant melanomas; sarcomas; and carcinomas of the colon, breast, cervix, endometrium, ovary, testis, nasopharynx, and kidney.

Natural killer (NK) cells are another population of effector cells with tumoricidal activity. In contrast to CTLs, NK cells lack the receptor for antigen detection but can still recognize normal cells infected with viruses or tumor cells. Their tumoricidal activity is termed natural because it is not induced by a specific antigen. The mechanism by which NK cells discriminate between normal and abnormal cells is under study. Evidence suggests that class I MHC molecules on the surface of normal cells inhibit NK cells and prevent lysis. Thus, the decreased level of class I molecule expression characteristic of many tumor cells may allow activation of NK cells and subsequent tumor lysis.

Macrophages can kill specific tumor cells when activated by a combination of factors, including lymphokines (soluble factors produced by T cells) and interferon. They are less effective than T-cell-mediated cytotoxic mechanisms. Under certain circumstances, macrophages may present TAAs to T cells and stimulate tumor-specific immune response.

Dendritic cells are dedicated antigen-presenting cells present in barrier tissues (eg, skin, lymph nodes). They play a central role in initiation of tumor-specific immune response. These cells take up tumor-associated proteins, process them, and present TAAs to T cells to stimulate the CTL response against tumor. The presence of dendritic cells in tumor tissues correlates with improved prognosis.

Lymphokines produced by immune cells stimulate growth or induce activities of other immune cells. Such lymphokines include IL-2, also known as T-cell growth factor, and the interferons. IL-12 is produced by dendritic cells and specifically induces CTLs, thereby enhancing antitumor immune responses.

Regulatory T cells are normally present in the body and help prevent autoimmune reactions. They are produced during the active phase of immune responses to pathogens and limit the strong immune response that could damage the host. Accumulation of these cells in cancers inhibits antitumor immune responses.

Myeloid-derived suppressor cells consist of immature myeloid cells and their precursors. These cells accumulate in large numbers in cancers and potently suppress immune responses.

Humoral Immunity

In contrast to T-cell cytotoxic immunity, humoral antibodies do not appear to confer significant protection against tumor growth. Most antibodies cannot recognize TAAs. Regardless, humoral antibodies that react with tumor cells in vitro have been detected in the sera of patients with various tumors, including Burkitt's lymphoma; malignant melanoma; osteosarcoma; neuroblastoma; and carcinomas of the lung, breast, and GI tract.

Cytotoxic antibodies are directed against surface antigens of tumor cells. These antibodies can exert anti-tumor effects through complement fixation or by serving as a flag for destruction of tumor cells by T cells (antibody-dependent cell-mediated cytotoxicity). Another population of humoral antibodies, called enhancing antibodies (blocking antibodies), may actually favor rather than inhibit tumor growth. The mechanisms and relative importance of such immunologic enhancement are not well understood.

Failure of Host Defenses

Although many tumors are eliminated by the immune system (and thus are never detected), others continue to grow despite the presence of TAAs. Several mechanisms have been proposed to explain this deficient host response to the TAA, including the following:

- Specific immunologic tolerance to TAAs in a process that involves antigen-presenting cells and suppressor T cells, possibly secondary to prenatal exposure to the antigen

- Suppression of immune response by chemical, physical, or viral agents (eg, helper T-cell destruction by HIV)

- Suppression of the immune response by cytotoxic drugs or radiation

- Suppression of the immune response by the tumor itself through various complex and largely uncharacterized mechanisms that cause various problems including decreased T, B, and antigen-presenting cell function, decreased IL-2 production, and increased circulating soluble IL-2 receptors (which bind and hence inactivate IL-2)

Tumor Immunodiagnosis

Tumor-associated antigens (TAAs) can help diagnose various tumors and sometimes determine the response to therapy or recurrence. An ideal tumor marker would be released only from tumor tissue, be specific for a given tumor type, be detectable at low levels of tumor cell burden, have a direct relationship to the tumor cell burden, and be present in all patients with the tumor. However, although most tumors release detectable antigenic macromolecules into the circulation, no tumor marker has all the requisite characteristics to provide enough specificity or sensitivity to be used in early diagnosis or mass cancer screening programs.

Carcinoembryonic antigen (CEA) is a protein-polysaccharide complex present in colon carcinomas and in normal fetal intestine, pancreas, and liver. Blood levels are elevated in patients with colon carcinoma, but the specificity is relatively low because positive results also occur in heavy cigarette smokers and in patients with cirrhosis, ulcerative colitis, and other cancers (eg, breast, pancreas, bladder, ovary, cervix). Monitoring CEA levels may be useful for detecting cancer recurrence after tumor excision if the patient initially had an elevated CEA and for refining estimates of prognosis by stage.

α-Fetoprotein, a normal product of fetal liver cells, is also present in the sera of patients with primary hepatoma, nonseminomatous germ cell tumors, and, frequently, ovarian or testicular embryonal carcinoma. Levels are sometimes useful for estimating prognosis or, less often, for diagnosis.

β Subunit of human chorionic gonadotropin (β-hCG), measured by immunoassay, is the major clinical marker in women with gestational trophoblastic neoplasia (GTN)—a disease spectrum that includes hydatidiform mole, nonmetastatic GTN, and metastatic GTN (see also p. 2574)—and in about two thirds of men with testicular embryonal carcinoma or choriocarcinoma. The β subunit is measured because it is specific for hCG. This marker is present in low levels in healthy people. Levels are elevated during pregnancy.

Prostate-specific antigen (PSA), a glycoprotein located in ductal epithelial cells of the prostate gland, can be detected in low concentrations in the sera of healthy men. Using an appropriate upper limit of normal, assays with monoclonal antibodies detect elevated serum levels of PSA in about 90% of patients with advanced prostate cancer, even in the absence of defined metastatic disease. It is more sensitive than prostatic acid phosphatase. However, because PSA is elevated in other conditions (eg, benign prostatic hypertrophy, prostatitis, recent GU tract instrumentation), it is less specific. PSA can be used to monitor recurrence after prostatic carcinoma has been diagnosed and treated.

CA 125 is clinically useful for screening, diagnosing, and monitoring therapy for ovarian cancer, although any peritoneal inflammatory process and some other cancers can increase levels.

β_2-Microglobulin is often elevated in multiple myeloma and in some lymphomas. Its primary use is in prognosis.

CA 19-9 was originally developed to detect colorectal cancer but proved more sensitive for pancreatic cancer. It is primarily used to judge the response to treatment in patients with advanced pancreatic cancers. CA 19-9 can also be elevated in other GI cancers, particularly cancer of the bile ducts, and

some benign bile duct and cholestatic disorders.

CA 15-3 and **CA 27-29** are elevated in most patients with metastatic breast cancer. Levels may also be elevated in other conditions. These markers are primarily used to monitor the response to therapy.

Chromogranin A is used as a marker for carcinoid and other neuroendocrine tumors. Sensitivity and specificity for neuroendocrine tumors can exceed 75%, and diagnostic accuracy is higher with diffuse than with localized tumors. Levels can be elevated in other cancers, such as lung and prostate, and some benign disorders (eg, primary hypertension, chronic kidney disease, chronic atrophic gastritis).

Thyroglobulin is produced by the thyroid and may be elevated with various thyroid disorders. It is primarily used after complete thyroidectomy to detect recurrent thyroid cancer and to monitor the response to treatment in metastatic thyroid cancer.

TA-90 is a highly immunogenic subunit of a urinary tumor-associated antigen that is present in 70% of melanomas, soft-tissue sarcomas, and carcinomas of the breast, colon, and lung. Some studies have shown that TA-90 levels can accurately predict survival and the presence of subclinical disease after surgery for melanoma.

Immunotherapy

A number of immunologic interventions, both passive and active, can be directed against tumor cells.

Passive Cellular Immunotherapy

In passive cellular immunotherapy, specific effector cells are directly infused and are not induced or expanded within the patient.

Lymphokine-activated killer (LAK) cells are produced from the patient's endogenous T cells, which are extracted and grown in a cell culture system by exposing them to the lymphokine IL-2. The proliferated LAK cells are then returned to the patient's bloodstream. Animal studies have shown that LAK cells are more effective against cancer cells than are the original endogenous T cells, presumably because of their greater number. Clinical trials of LAK cells in humans are ongoing.

Tumor-infiltrating lymphocytes (TILs) may have greater tumoricidal activity than LAK cells. These cells are grown in culture in a manner similar to LAK cells. However, the progenitor cells consist of T cells that are isolated from resected tumor tissue. This process theoretically provides a line of T cells that has greater tumor specificity than those obtained from the bloodstream. Recent clinical studies have shown highly promising results.

Concomitant use of interferon enhances the expression of major histocompatibility complex (MHC) antigens and tumor-associated antigens (TAAs) on tumor cells, thereby augmenting the killing of tumor cells by the infused effector cells.

However, remissions using unmodified TILs have been infrequent. A new approach using T cells genetically modified to express receptors that recognize TAAs with high specificity to tumor cells is under study and may provide significant clinical benefit.

Passive Humoral Immunotherapy

Administration of exogenous antibodies constitutes passive humoral immunotherapy. Antilymphocyte serum has been used in the treatment of chronic lymphocytic leukemia and in T-cell and B-cell lymphomas, resulting in temporary decreases in lymphocyte counts or lymph node size.

Monoclonal antitumor antibodies may also be conjugated with toxins (eg, ricin, diphtheria) or with radioisotopes so that the antibodies deliver these toxic agents specifically to the tumor cells. Another technique involves bispecific antibodies, or linkage of one antibody that reacts with the tumor cell to a second antibody that reacts with a cytotoxic effector cell. This technique brings the effector cell in close

opposition to the tumor cell, resulting in increased tumoricidal activity. However, these techniques are in early stages of testing; thus, potential clinical benefits are uncertain.

Active Specific Immunotherapy

Inducing cellular immunity (involving cytotoxic T cells) in a host that failed to spontaneously develop an effective response generally involves methods to enhance presentation of tumor antigens to host effector cells. Cellular immunity can be induced to specific, very well-defined antigens. Several techniques can be used to stimulate a host response; these techniques may involve giving peptides, DNA, or tumor cells (from the host or another patient). Peptides and DNA are often given using antigen-presenting cells (dendritic cells). These dendritic cells can also be genetically modified to secrete additional immune-response stimulants (eg, granulocyte-macrophage colony-stimulating factor [GM-CSF]).

Peptide-based vaccines use peptides from defined TAAs. An increasing number of TAAs have been identified as the target of T cells in cancer patients and are being tested in clinical trials. Recent data indicate that responses are most potent if TAAs are delivered using dendritic cells. These cells are obtained from the patient, loaded with the desired TAA, and then reintroduced intradermally; they stimulate endogenous T cells to respond to the TAA. The peptides also can be delivered by co-administration with immunogenic adjuvants.

DNA vaccines use recombinant DNA that encodes a specific (defined) antigenic protein. The DNA is incorporated into viruses that are injected directly into patients or, more often, introduced into dendritic cells obtained from the patients, which are then injected back into them. The DNA expresses the target antigen which triggers or enhances patients' immune response.

Autochthonous tumor cells (cells taken from the host) have been reintroduced to the host after use of ex vivo techniques (eg, irradiation, neuraminidase treatment, hapten conjugation, hybridization with other cell lines) to reduce their malignant potential and increase their antigenic activity. Sometimes the tumor cells are genetically modified to produce immunostimulatory molecules (including cytokines such as GM-CSF or IL-2, costimulatory molecules such as B7-1, and allogeneic class I MHC molecules); this modification helps attract effector molecules and enhances systemic tumor targeting. Clinical trials with GM-CSF-modified tumor cells have produced encouraging preliminary results.

Allogeneic tumor cells (cells taken from other patients) have been used in patients with acute lymphocytic leukemia and acute myeloblastic leukemia. Remission is induced by intensive chemotherapy and radiation therapy. Then, irradiated allogeneic tumor cells that have been modified either genetically or chemically to increase their immunogenic potential are injected into the patient. Sometimes patients are also given bacille Calmette-Guerin (BCG) vaccine or other adjuvants (see p. 1061) to enhance the immune response against the tumor. Prolonged remissions or improved reinduction rates have been reported in some series but not in most.

A novel approach to cancer treatment combining immunotherapy and conventional chemotherapy has shown some success (vs historic controls) in nonrandomized phase I and phase II clinical trials involving various cancers, types of vaccines, and chemotherapy.

Nonspecific Immunotherapy

Interferons (IFN-α, -β, -γ) are glycoproteins that have antitumor and antiviral activity. Depending on dose, interferons may either enhance or decrease cellular and humoral immune functions. Interferons also inhibit division and certain synthetic processes in a variety of cells. Clinical trials have indicated that interferons have antitumor activity in various cancers, including hairy cell leukemia, chronic myelocytic leukemia, AIDS-associated Kaposi's sarcoma, non-Hodgkin lymphoma, multiple myeloma, and ovarian carcinoma. However, interferons may have significant adverse effects, such as fever, malaise, leukopenia, alopecia, and myalgias.

Certain **bacterial adjuvants** (BCG and derivatives, killed suspensions of *Corynebacterium parvum*) have tumoricidal properties. They have been used with or without added tumor antigen to treat a variety of cancers, usually along with intensive chemotherapy or radiation therapy. For example, direct injection of

BCG into cancerous tissues has resulted in regression of melanoma and prolongation of disease-free intervals in superficial bladder carcinomas and may help prolong drug-induced remission in acute myeloblastic leukemia, ovarian carcinoma, and non-Hodgkin lymphoma.

Chapter 124. Principles of Cancer Therapy

Introduction

Curing cancer requires eliminating all cancer cells. The major modalities of therapy are

• Surgery and radiation therapy (for local and local-regional disease)

• Chemotherapy (for systemic disease) Other important methods include

• Hormonal therapy (for selected cancers, eg, prostate, breast, endometrium)

• Immunotherapy (monoclonal antibodies, interferons, and other biologic response modifiers and tumor vaccines—see p. 1059)

• Differentiating agents such as retinoids

• Targeted agents that exploit the growing knowledge of cellular and molecular biology

Overall treatment should be coordinated among a radiation oncologist, surgeon, and medical oncologist, where appropriate. Choice of modalities constantly evolves, and numerous controlled research trials continue. When available and appropriate, clinical trial participation should be considered and discussed with patients.

Various terms are used to describe the response to treatment (see Table 124-1). The disease-free interval often serves as an indicator of cure and varies with cancer type. For example, lung, colon, bladder, and testicular cancers are usually cured if a 5-yr disease-free interval occurs. However, breast cancer may recur even after 5 yr; thus a 10-yr disease-free interval is more indicative of cure.

Treatment decisions should weigh the likelihood of adverse effects against the likelihood of benefit; these decisions require frank communication and possibly the involvement of a multidisciplinary cancer team. Patient preferences for how to live out the end of life should be established early in the course of cancer

[**Table 124-1.** Defining Response to Cancer Treatment]

treatment despite the difficulties of discussing death at such a sensitive time (see p. 3471).

Modalities of Cancer Therapy

Treatment of cancer can involve any of several modalities:

• Surgery

• Radiation therapy

• Chemotherapy

Often, modalities are combined to create a program that is appropriate for the patient and is based on patient and tumor characteristics as well as patient preferences.

Survival rates with the different modalities, alone and in combination, are listed for selected cancers (see Table 124-2).

Surgery

Surgery is the oldest form of effective cancer therapy. It may be used alone or in combination with other modalities.

Factors that increase operative risk in cancer patients include

• Age

• Comorbid conditions

• Debilitation due to cancer

• Paraneoplastic syndromes (less common—see p. 1054)

Cancer patients often have poor nutrition due to anorexia and the catabolic influences of tumor growth, and these factors may inhibit or slow recovery from surgery. Patients may be neutropenic or thrombocytopenic or may have clotting disorders; these conditions increase the risk of sepsis and hemorrhage. Therefore, preoperative assessment is paramount (see p. 3445).

[**Table 124-2.** 5-yr Disease-Free Survival Rates by Cancer Therapy]

Primary tumor resection: If a primary tumor has not metastasized, surgery may be curative. Establishing a complete margin of normal tissue around the primary tumor is critical for the success of primary tumor resection. Intraoperative examination of frozen tissue sections by a pathologist may be needed, with immediate resection of additional tissue if margins are positive for tumor cells. However, frozen tissue examination is inferior to examination of processed and stained tissue. Later review of margin tissue may prove the need for wider resection.

Surgical resection for primary tumor with local spread may also require removal of involved regional lymph nodes, resection of an involved adjacent organ, or en bloc resection. Survival rates with surgery alone are listed for selected cancers (see Table 124-2).

When the primary tumor has spread into adjacent normal tissues extensively, surgery may be delayed so that other modalities (eg, chemotherapy, radiation therapy) can be used to reduce the size of the required resection.

Resection of metastases: With regional lymph node metastases, nonsurgical modalities may be the best initial treatments, as in locally advanced lung cancer or head and neck cancer. Single metastases, especially those in the lung, can sometimes be resected with a reasonable rate of cure.

Patients with a limited number of metastases, particularly to the liver, brain, or lungs, may benefit from surgical resection of both the primary and metastatic tumor. For example, in colon cancer with liver metastases, resection produces 5-yr survival rates of 30 to 40% if < 4 hepatic lesions exist and if adequate tumor margins can be obtained.

Cytoreduction: Cytoreduction (surgical resection to reduce tumor burden) is often an option when removal of all tumor tissue is impossible, as in most cases of ovarian cancer. Cytoreduction may increase the sensitivity of the remaining tissue to other treatment modalities through mechanisms that are not entirely clear. Cytoreduction has yielded favorable results in pediatric solid tumors and in ovarian cancer.

Palliative surgery: Surgery to relieve symptoms and preserve quality of life may be a reasonable alternative when cure is unlikely or when an attempt at cure produces adverse effects that are unacceptable to the patient. Tumor resection may be indicated to control pain, to reduce the risk of hemorrhage, or to relieve obstruction of a vital organ (eg, intestine, urinary tract). Nutritional supplementation with a feeding gastrostomy or jejunostomy tube may be necessary if proximal obstruction exists.

Reconstructive surgery: Reconstructive surgery may improve a patient's comfort or quality of life after tumor resection (eg, breast reconstruction after mastectomy).

Radiation Therapy

Radiation therapy can cure many cancers (see Table 124-2), particularly those that are localized or that can be completely encompassed within the radiation field. Radiation therapy with surgery (for head and neck, laryngeal, or uterine cancer) or with chemotherapy and surgery (for sarcomas or breast, esophageal, lung, or rectal cancers) improves cure rates and allows for more limited surgery as compared with traditional surgical resection.

Radiation therapy can provide significant palliation when cure is not possible:

• For brain tumors: Prolongs patient functioning

• For cancers that compress the spinal cord: Prevents progression of neurologic deficits

• For superior vena cava syndromes: Relieves venous obstruction

• For painful bone lesions: Usually relieves symptoms

Radiation cannot destroy malignant cells without destroying some normal cells as well. Therefore, the risk to normal tissue must be weighed against the potential gain in treating the malignant cells. The final outcome of a dose of radiation depends on numerous factors, including

• Nature of the delivered radiation (mode, timing, volume, dose)

• Properties of the tumor (cell cycle phase, oxygenation, molecular properties, overall sensitivity to radiation)

In general, cancer cells are selectively damaged because of their high metabolic rate. Normal tissue repairs itself more effectively, resulting in greater net destruction of tumor.

Important considerations in the use of radiation therapy include the following:

• Treatment timing (critical)

• Dose fractionation (critical)

• Normal tissue in or adjacent to the proposed radiation field

• Target volume

• Configuration of radiation beams

• Dose distribution

• Modality and energy most suited to the patient's situation

Treatment is tailored to take advantage of the cellular kinetics of tumor growth, with the aim of maximizing damage to the tumor while minimizing damage to normal tissues.

Radiation therapy sessions begin with the precise positioning of the patient. Foam casts or plastic masks are often constructed to ensure exact repositioning for serial treatments. Laser-guided sensors are used. Typical courses consist of large daily doses given over 3 wk for palliative treatment or smaller doses given once/day 5 days/wk for 6 to 8 wk for curative treatment.

Types of radiation therapy: There are several different types of radiation therapy.

External beam radiation therapy can be done with photons (gamma radiation), electrons, or protons. Gamma radiation using a linear accelerator is the most common type of radiation therapy. The radiation dose to adjacent normal tissue can be limited by conformal technology, which reduces scatter at the field

margins. Electron beam radiation therapy produces little tissue penetration and is best for skin or superficial cancers. Different energies of electrons are used based on the desired depth of penetration and type of tumor. Proton therapy, although limited in availability, can provide sharp margins and is particularly useful for tumors of the eye, the base of the brain, and the spine.

Stereotactic radiation therapy is radio-surgery with precise stereotactic localization of a tumor to deliver a single high dose or multiple, fractionated doses to a small intracranial or other target. Advantages include complete tumor ablation where conventional surgery would not be possible and minimal adverse effects. Disadvantages include limitations involving the size of the area that can be treated and the potential danger to adjacent tissues because of the high dose of radiation. In addition, it cannot be used in all areas of the body. Patients must be immobilized and the area kept completely still.

Brachytherapy involves placement of radioactive seeds into the tumor bed itself (eg, in the prostate or cervix). Typically, placement is guided by CT or ultrasonography. Brachytherapy achieves higher effective radiation doses over a longer period than could be accomplished by use of fractionated, external irradiation.

Systemic radioactive isotopes can direct radiation to cancer in organs that have specific receptors for uptake of the isotope (ie, radioactive iodine for thyroid cancer) or when the radionuclide is attached to a monoclonal antibody (eg, tositumomab plus iodine-131 tositumomab for non-Hodgkin lymphoma). Isotopes can also accomplish palliation of generalized bony metastases (ie, radiostrontium for prostate cancer).

Other agents or strategies, particularly chemotherapy, can sensitize tumor tissue to the delivered radiation and increase efficacy.

Adverse effects: Radiation can damage any intervening normal tissue.

Acute adverse effects depend on the area receiving radiation and may include

- Lethargy
- Fatigue
- Mucositis
- Dermatologic manifestations (erythema, pruritus, desquamation)
- Esophagitis
- Pneumonitis
- Hepatitis
- GI symptoms (nausea, vomiting, diarrhea, tenesmus)
- GU symptoms (frequency, urgency, dysuria)
- Cytopenias

Early detection and management of these adverse effects is important not only for the patient's comfort and quality of life but also to ensure continuous treatment; prolonged interruption can allow for tumor regrowth.

Late complications can include cataracts, keratitis, and retinal damage if the eye is in the treatment field; hypopituitarism; xerostomia; hypothyroidism; pneumonitis; pericarditis; esophageal stricture; hepatitis; ulcers; gastritis; nephritis; sterility; and muscular contractures. Radiation that reaches normal tissue can lead to poor healing of the tissues if further procedures or surgery is necessary. For example,

radiation to the head and neck impairs recovery from dental procedures (eg, restoration, extraction) and thus should be administered only after all necessary dental work has been done.

Radiation therapy can increase the risk of developing other cancers, particularly leukemias and cancers of the thyroid or breast. Peak incidence occurs 5 to 10 yr after exposure and depends on the patient's age at the time of treatment. For example, chest irradiation for Hodgkin lymphoma in adolescent girls leads to a higher risk of breast cancer than does the same treatment for postadolescent women.

Chemotherapy

The ideal chemotherapeutic drug would target and destroy only cancer cells. Only a few such drugs exist. Common chemotherapeutic drugs and their adverse effects are described (see Table 124-3).

The most common routes of administration are IV and oral. Frequent dosing for extended

[**Table 124-3.** Commonly Used Antineoplastic Drugs]

periods may necessitate subcutaneously implanted venous access devices (central or peripheral), multilumen external catheters, or peripherally inserted central catheters.

Drug resistance can occur to chemotherapy. Identified mechanisms include overexpression of target genes, mutation of target genes, drug inactivation by tumor cells, defective apoptosis in tumor cells, and loss of receptors for hormonal agents. One of the best characterized mechanisms is overexpression of the *MDR-1* gene, a cell membrane transporter that causes efflux of certain drugs (eg, vinca alkaloids, taxanes, anthracyclines). Attempts to alter *MDR-1* function and thus prevent drug resistance have been unsuccessful.

Cytotoxic drugs: Traditional cytotoxic chemotherapy, which damages cell DNA, kills many normal cells in addition to cancer cells. Antimetabolites, such as 5-fluorouracil and methotrexate, are cell cycle-specific and have no linear dose-response relationship. In contrast, other chemotherapeutic drugs (eg, DNA cross-linkers, also known as alkylating agents) have a linear dose-response relationship, producing more tumor killing as well as more toxicity at higher doses. At their highest doses, DNA cross-linkers may produce bone marrow aplasia, necessitating bone marrow transplantation to restore bone marrow function.

Single-drug chemotherapy may cure selected cancers (eg, choriocarcinoma, hairy cell leukemia). More commonly, multidrug regimens incorporating drugs with different mechanisms of action and different toxicities are used to increase the tumor cell kill, reduce dose-related toxicity, and decrease the probability of drug resistance. These regimens can provide significant cure rates (eg, in acute leukemia, testicular cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, and, less commonly, solid tumors such as small cell lung cancer and nasopharyngeal cancer). Multidrug regimens typically are given as repetitive cycles of a fixed combination of drugs. The interval between cycles should be the shortest one that allows for recovery of normal tissue. Continuous infusion may increase cell kill with some cell cycle-specific drugs (eg, 5-fluorouracil).

For each patient, the probability of significant toxicities should be weighed against the likelihood of benefit. End-organ function should be assessed before chemotherapeutic drugs with organ-specific toxicities are used (eg, echocardiography before doxorubicin use). Dose modification or exclusion of certain drugs may be necessary in patients with chronic lung disease (eg, bleomycin), renal failure (eg, methotrexate), or hepatic dysfunction (eg, taxanes).

Despite these precautions, adverse effects commonly result from cytotoxic chemotherapy. The normal tissues most commonly affected are those with the highest intrinsic turnover rate: bone marrow, hair follicles, and the GI epithelium.

Imaging (eg, CT, MRI, PET) is frequently done after 2 to 3 cycles of therapy to evaluate response to treatment. Therapy continues if there is a clear response. If the tumor progresses despite therapy, the

regimen is often amended or stopped. If the disease remains stable with treatment and the patient can tolerate therapy, then a decision to continue is reasonable with the understanding that the disease will eventually progress.

Hormonal therapy: Hormonal therapy uses hormone agonists or antagonists to influence the course of cancer. It may be used alone or in combination with other treatment modalities.

Hormonal therapy is particularly useful in prostate cancer, which grows in response to androgens. Other cancers with hormone receptors on their cells (eg, breast, endometrium) can often be palliated by hormone antagonist therapy or hormone ablation.

Use of prednisone, a glucocorticosteroid, is also considered hormonal therapy. It is frequently used to treat tumors derived from the immune system (lymphomas, lymphocytic leukemias, multiple myeloma).

Biologic response modifiers: Interferons are proteins synthesized by cells of the immune system as a physiologic immune protective response to foreign antigens (viruses, bacteria, other foreign cells). In pharmacologic amounts, they can palliate some cancers, including hairy cell leukemia, chronic myelocytic leukemia, locally advanced melanoma, metastatic renal cell cancer, and Kaposi's sarcoma. Significant toxic effects of interferon include fatigue, depression, nausea, leukopenia, chills and fever, and myalgias.

Interleukins, primarily the lymphokine IL-2 produced by activated T cells, can be used in metastatic melanomas and can provide modest palliation in renal cell cancer.

Differentiating drugs: These drugs induce differentiation in cancer cells. All-*trans*-retinoic acid has been highly effective in treating acute promyelocytic leukemia. Other drugs in this class include arsenic compounds and the hypomethylating agents azacytidine and deoxyazacytidine. When used alone, these drugs have only transient effects, but their role in prevention and in combination with cytotoxic drugs is promising.

Antiangiogenesis drugs: Solid tumors produce growth factors that form new blood vessels necessary to support ongoing tumor growth. Several drugs that inhibit this process are available. Thalidomide is antiangiogenic, among its many effects. Bevacizumab, a monoclonal antibody to vascular endothelial growth factor (VEGF), is effective against renal cancers and colon cancer. VEGF receptor inhibitors are also affective in renal cancer, hepatocellular cancers, and GI stromal tumors.

Signal transduction inhibitors: Many epithelial tumors possess mutations that activate signaling pathways that cause their continuous proliferation and failure to differentiate. These mutated pathways include growth factor receptors and the downstream proteins that transmit messages to the cell nucleus from growth factor receptors on the cell surface. Three such drugs, imatinib (an inhibitor of the BCR-ABL tyrosine kinase in chronic myelocytic leukemia) and erlotinib and gefitinib (inhibitors of the epidermal growth factor receptor), are now in routine clinical use. Other inhibitors of these signaling pathways are under study.

Monoclonal antibodies: Monoclonal antibodies directed against unique tumor antigens have some efficacy against neoplastic tissue (see also p. 1060). Trastuzumab, an antibody directed against a protein called Her-2 or Erb-B2, plus chemotherapy has shown benefit in metastatic breast cancer. Antibodies against CD antigens expressed on neoplastic cells, such as CD20 and CD33, are used to treat patients with non-Hodgkin lymphoma (rituximab, anti-CD20 antibody) and acute myelocytic leukemia (gemtuzumab, an antibody linked to a potent toxin).

The effectiveness of monoclonal antibodies may be increased by linking them to radioactive nuclide. One such drug, ibritumomab, is used to treat non-Hodgkin lymphoma.

Multimodality and Adjuvant Chemotherapy

In some tumors with a high likelihood of relapse despite optimal initial surgery or radiation therapy, relapse may be prevented by addition of adjuvant chemotherapy. Increasingly, combined-modality therapy (eg, radiation therapy, chemotherapy, surgery) is used. It may permit organ-sparing procedures and

preserve organ function.

Adjuvant therapy: Adjuvant therapy is systemic chemotherapy or radiation therapy given to eradicate residual occult tumor after initial surgery. Patients who have a high risk of recurrence may benefit from its use. General criteria are based on degree of local extension of the primary tumor, presence of positive lymph nodes, and certain morphologic or biologic characteristics of individual cancer cells. Adjuvant therapy has increased disease-free survival and cure rate in breast and in colorectal cancer.

Neoadjuvant therapy: Neoadjuvant therapy is chemotherapy, radiation therapy, or both given *before* surgical resection. This treatment may enhance resectability and preserve local organ function. For example, when this therapy is used in head and neck, esophageal, or rectal cancer, a smaller subsequent resection may be possible. Another advantage of neoadjuvant therapy is in assessing response to treatment; if the primary tumor does not respond, micrometastases are unlikely to be eradicated, and an alternate regimen should be considered. Neoadjuvant therapy may obscure the true pathologic stage of the cancer by altering tumor size and margins and converting histologically positive nodes to negative, complicating clinical staging. The use of neoadjuvant therapy has improved survival in inflammatory and locally advanced breast, stage IIIA lung, nasopharyngeal, and bladder cancers.

Bone Marrow Transplantation

Bone marrow or stem cell transplantation is an important component of the treatment of otherwise refractory lymphomas, leukemias, and multiple myeloma (for an in-depth discussion of this topic, see p. 1132).

Gene Therapy

Genetic modulation is under intense investigation. Strategies include the use of antisense therapy, systemic viral vector transfection, DNA injection into tumors, genetic modulation of resected tumor cells to increase their immunogenicity, and alteration of immune cells to enhance their antitumor response.

Management of Adverse Effects

Patients being treated for cancer frequently experience adverse effects. Managing these effects improves quality of life.

Nausea and Vomiting

Nausea and vomiting are commonly experienced by cancer patients and may result from the cancer itself (eg, paraneoplastic syndromes) or from its treatment (eg, chemotherapy, radiation therapy to the brain or abdomen). However, refractory nausea and vomiting should prompt further investigation, including basic laboratory testing (electrolytes, liver function tests, lipase) and x-rays to investigate possible bowel obstruction or intracranial metastases.

Serotonin-receptor antagonists are the most effective drugs but are also the most expensive. Virtually no toxicity occurs with granisetron and ondansetron aside from headache and orthostatic hypotension. A 0.15-mg/kg dose of ondansetron or a 10-µg/kg dose of granisetron is given IV 30 min before chemotherapy. Doses of ondansetron can be repeated 4 and 8 h after the first dose. The efficacy against highly emetogenic drugs, such as the platinum complexes, can be improved with co-administration of dexamethasone (8 mg IV given 30 min before chemotherapy with repeat doses of 4 mg IV q 8 h).

A substance P/neurokinin-1 antagonist, aprepitant, can limit nausea and vomiting resulting from highly emetogenic chemotherapy. Dosage is 125 mg po 1 h before chemotherapy on day 1, then 80 mg po 1 h before chemotherapy on days 2 and 3.

Other traditional antiemetics, including phenothiazines (eg, prochlorperazine 10 mg IV q 8 h, promethazine 12.5 to 25 mg po or IV q 8 h) and metoclopramide (10 mg po or IV given 30 min before chemotherapy with repeated doses q 6 to 8 h), are alternatives restricted to patients with mild to moderate nausea and vomiting.

Dronabinol (Δ-9-tetrahydrocannabinol [THC]) is an alternative treatment for nausea and vomiting caused by chemotherapy. THC is the principal psychoactive component of marijuana. Its mechanism of antiemetic action is unknown, but cannabinoids bind to opioid receptors in the forebrain and may indirectly inhibit the vomiting center. Dronabinol is administered in doses of 5 mg/m^2 po 1 to 3 h before chemotherapy, with repeated doses q 2 to 4 h after the start of chemotherapy (maximum of 4 to 6 doses/day). However, it has variable oral bioavailability, is not effective for inhibiting the nausea and vomiting of platinum-based chemotherapy regimens, and has significant adverse effects (eg, drowsiness, orthostatic hypotension, dry mouth, mood changes, visual and time sense alterations). Smoking marijuana may be more effective. Marijuana for this purpose can be obtained legally in some states. It is used less commonly because of barriers to availability and because many patients cannot tolerate smoking.

Benzodiazepines, such as lorazepam (1 to 2 mg po or IV given 10 to 20 min before chemotherapy with repeated doses q 4 to 6 h prn), are sometimes helpful for refractory or anticipatory nausea and vomiting.

Cytopenias

Anemia, leukopenia, and thrombocytopenia may develop during chemotherapy or radiation therapy.

Anemia: Clinical symptoms and decreased efficacy of radiation therapy usually occur at Hct levels of < 30% or Hb levels < 10 g/dL, sooner in patients with coronary artery disease or peripheral vascular disease. Recombinant erythropoietin therapy may be started when Hb falls to < 10 mg/dL, depending on symptoms. In general, 150 to 300 units/kg sc 3 times/wk (a convenient adult dose is 10,000 units) is effective and reduces the need for transfusions. Longer-acting formulations of erythropoietin require less frequent dosing (darbepoetin alfa 2.25 to 4.5 µg/kg sc q 1 to 2 wk). Unnecessary use of erythropoietin should be avoided. Packed RBC transfusions may be needed to relieve acute cardiorespiratory symptoms.

Thrombocytopenia: A platelet count < 10,000/mL, especially with bleeding, requires transfusion of platelet concentrates. Small molecules that mimic thrombopoietin are available but are not commonly used in cancer treatment.

Leukocyte depletion of transfused blood products may prevent alloimmunization to platelets and should be used in patients who are expected to need platelet transfusions during multiple courses of chemotherapy or for candidates for bone marrow or stem cell transplantation. Leukocyte depletion also lowers the probability of cytomegalovirus being transferred to the patient through WBCs. Gamma irradiation of blood products to inactivate lymphocytes and prevent transfusion-induced graft-vs-host disease is also indicated in patients undergoing severely immunosuppressive chemotherapy.

Neutropenia: Neutropenia (see also p. 948), usually defined by an absolute neutrophil count < 500/µL, predisposes to immediate life-threatening infection.

Afebrile patients with neutropenia require close outpatient follow-up for detection of fever and should be instructed to avoid contact with sick people or areas frequented by large numbers of people (eg, shopping malls, airports). Although most patients do not require antibiotics, patients with severe immunosuppression (ie, concomitant T-cell depletion or loss of function) *and* leukopenia are sometimes given trimethoprim/sulfamethoxazole (one double-strength tablet/day) as prophylaxis for *Pneumocystis jiroveci*. In transplant patients or others receiving high-dose chemotherapy, antiviral prophylaxis (acyclovir 800 mg po bid or 400 mg IV q 12 h) should be considered if serologic tests are positive for herpes simplex virus.

Fever > 38° C in a patient with neutropenia is an emergency. Evaluation should include immediate chest x-ray and cultures of blood, sputum, urine, stool, and any suspect skin lesions. Examination includes possible abscess sites (eg, skin, ears), skin and mucosa for presence of herpetic lesions, retina for vascular lesions suggestive of metastatic infection, and catheter sites. Rectal examination and use of a rectal thermometer are avoided if possible in neutropenic patients because of the risk of bacteremia.

Febrile neutropenic patients should receive broad-spectrum antibiotics chosen on the basis of the most

likely source. Typical regimens include cefepime or ceftazidime 2 g IV q 8 h immediately after samples for culture are obtained. If diffuse pulmonary infiltrates are present, sputum should be tested for *P. jirovecii*, and if positive, appropriate therapy should be started. If fever resolves within 72 h after starting empiric antibiotics, then antibiotics are continued until the absolute neutrophil count is > 500/µL. If fever continues for 120 h, antifungal drugs should be added to treat possible fungal causes. Re-assessment for occult infection (often including CT of the chest and abdomen) should be undertaken at this time.

In selected patients with neutropenia related to chemotherapy, especially after high-dose chemotherapy, granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) may be started to shorten the leukopenic period. GCSF 5 µg/kg sc once/day up to 14 days and longer-acting forms (eg, pegfilgrastim 6 mg sc single dose once per chemotherapy cycle) may be used to accelerate WBC recovery. These drugs should not be administered in the first 24 h after chemotherapy, and for pegfilgrastim, at least 14 days should elapse until the next planned chemotherapy dose. These drugs are begun at the onset of fever or sepsis or, in afebrile patients, when neutrophil counts fall to < 500/µL.

Many centers use outpatient treatment of selected low-risk patients with fever and neutropenia. Candidates must not have hypotension, altered mental status, respiratory distress, uncontrolled pain, or serious comorbid illnesses, such as diabetes, heart disease, or hypercalcemia. The regimen in such cases requires daily follow-up and often involves visiting nurse services and home antibiotic infusion. Some regimens involve oral antibiotics, such as ciprofloxacin 750 mg po bid plus amoxicillin/clavulanate 875 mg po bid or 500 mg po tid. If no defined institutional program for follow-up and treatment of neutropenic fever is available in an outpatient setting, then hospitalization is required.

Gastrointestinal Effects

Oral lesions: Oral lesions, such as ulcers, infections, and inflammation, are common.

Oral candidiasis can be treated with nystatin oral suspension 5 to 10 mL qid, clotrimazole troches 10 mg qid, or fluconazole 100 mg po once/day.

Mucositis from radiation therapy can cause pain and preclude sufficient oral intake, leading to undernutrition and weight loss. Rinses with analgesics and topical anesthetics (2% viscous lidocaine, 5 to 10 mL q 2 h or other commercially available mixtures) before meals, a bland diet without citrus food or juices, and avoidance of temperature extremes may allow patients to eat and maintain weight. If not, a feeding tube may be helpful if the small intestine is functional. For severe mucositis and diarrhea or an abnormally functioning intestine, parenteral alimentation may be needed.

Diarrhea: Diarrhea from pelvic radiation therapy or from chemotherapy can be alleviated with antidiarrheal drugs as needed (kaolin/pectin suspension 60 to 120 mL regular strength, or 30 to 60 mL concentrate, po at first sign of diarrhea and after each loose stool or prn; loperamide 2 to 4 mg po; or diphenoxylate/atropine 1 to 2 tablets po). Patients who underwent abdominal surgery or received broad-spectrum antibiotics within the preceding 3 mo should undergo stool testing for *Clostridium difficile*.

Constipation: Constipation may result from opioid use. A stimulant laxative such as senna 2 to 6 tablets po at bedtime or bisacodyl 10 mg po at bedtime should be initiated when repeated opioid use is anticipated. Established constipation can be treated with various drugs (eg, bisacodyl 5 to 10 mg po q 12 to 24 h, milk of magnesia 15 to 30 mL po at bedtime, lactulose 15 to 30 mL q 12 to 24 h, Mg citrate 250 to 500 mL po once). Enemas and suppositories should be avoided in patients with neutropenia or thrombocytopenia.

Anorexia: Appetite may decrease secondary to cancer treatment or to a paraneoplastic syndrome. Corticosteroids (dexamethasone 4 mg po once/day, prednisone 5 to 10 mg po once/day) and megestrol acetate 400 to 800 mg once/day are most effective. However, the primary benefits are variably increased appetite and weight gain, not improved survival or quality of life.

Pain

Pain should be anticipated and aggressively treated (see also p. 1623). Use of multiple drug classes may provide better pain control with fewer or less severe adverse effects than single drug classes. NSAIDs should be avoided in patients with thrombocytopenia. Opioids are the mainstay of treatment, given around the clock in generally efficient doses, with supplemental doses given for occasional worse pain. If the oral route is unavailable, fentanyl is given transdermally. Antiemetics and prophylactic bowel regimens are often needed with opioids.

Neuropathic pain can be treated with gabapentin; the dose required is high (up to 3.6 g/day) but must be started low and then increased over a few weeks. Alternatively, a tricyclic antidepressant (eg, nortriptyline 25 to 75 mg po at bedtime) may be tried.

Useful nondrug treatments for pain include focal radiation therapy, nerve blockade, and surgery.

Depression

Depression is often overlooked. It may occur in response to the disease (its symptoms and feared consequences), adverse effects of the treatments, or both. Patients receiving interferon can develop depression as an adverse effect. Also, alopecia as an adverse effect of radiation therapy or chemotherapy can contribute to depression. Frank discussion of a patient's fears can often relieve anxiety; depression can often be treated effectively (see p. 1538).

Tumor Lysis Syndrome

Tumor lysis syndrome may occur secondary to release of intracellular components into the bloodstream as a result of tumor cell death after chemotherapy. It occurs mainly in acute leukemias and non-Hodgkin lymphomas but can also occur in other hematologic cancers and, uncommonly, after treatment of solid tumors. It should be suspected in patients with a large tumor burden who develop acute renal failure after initial treatment.

The diagnosis is confirmed by some combination of the following findings:

- Renal failure
- Hypocalcemia (< 8 mg/dL)
- Hyperuricemia (> 15 mg/dL)
- Hyperphosphatemia (> 8 mg/dL)

Allopurinol (200 to 400 mg/m^2 once/day, maximum 600 mg/day) and normal saline IV to achieve urine output > 2 L/day should be initiated with close laboratory and cardiac monitoring. Patients who have a cancer with rapid cell turnover should receive allopurinol for at least 2 days before and during chemotherapy; for patients with high cell burden, this regimen can be continued for 10 to 14 days after therapy. All such patients should receive vigorous IV hydration to establish a diuresis of at least 100 mL/h prior to treatment. Although some physicians advocate $NaHCO_3$ IV to alkalinize the urine and increase solubilization of uric acid, alkalinization may promote Ca phosphate deposition in patients with hyperphosphatemia, and a pH of about 7 should be avoided. Alternatively, rasburicase, an enzyme that oxidizes uric acid to allantoin (a more soluble molecule), may be used to prevent tumor lysis. The dose is 0.15 to 0.2 mg/kg IV over 30 min once/day for 5 to 7 days, typically initiated 4 to 24 h before the first chemotherapy treatment. Adverse effects may include anaphylaxis, hemolysis, hemoglobinuria, and methemoglobinemia.

Cachexia

Cachexia is wasting of both adipose and skeletal muscle. It occurs in many conditions and is common with many cancers when remission or control fails. Some cancers, especially pancreatic and gastric cancers, cause profound cachexia. Affected patients may lose 10 to 20% of body weight. Men tend to

experience worse cachexia with cancer than do women. Neither tumor size nor the extent of metastatic disease predicts the degree of cachexia. Cachexia is associated with reduced response to chemotherapy, poor functional performance, and increased mortality.

The primary cause of cachexia is not anorexia or decreased caloric intake. Rather, this complex metabolic condition involves increased tissue catabolism. Protein synthesis is decreased and degradation increased. Cachexia is mediated by certain cytokines, especially tumor necrosis factor-α, IL-1b, and IL-6, which are produced by tumor cells and host cells in the tissue mass. The ATP-ubiquitin-protease pathway plays a role as well.

Cachexia is easy to recognize, primarily by weight loss, which is most apparent with loss of temporalis muscle mass in the face. The loss of subcutaneous fat increases the risk of pressure ulcers over bony prominences.

Treatment

Treatment involves treatment of the cancer. If the cancer can be controlled or cured, regardless of modality, cachexia resolves.

Additional caloric supplementation does not relieve cachexia. Any weight gain is usually minimal and is likely to consist of adipose tissue rather than muscle. Neither function nor prognosis is improved. Thus, in most cachectic patients with cancer, high-calorie supplementation is not recommended, and parenteral nutritional support is not indicated, except in situations where oral intake of adequate nutrition is impossible.

However, other treatments can mitigate cachexia and improve function. Corticosteroids increase appetite and may improve a sense of well-being but do little to increase body weight. Likewise, cannabinoids (marijuana, dronabinol) increase appetite but not weight. Progestogens, such as megestrol acetate, 40 mg po bid or tid, may increase both appetite and body weight. Drugs to alter cytokine production and effects are being studied.

Incurable Cancer

Even in cases of incurable cancer, palliative or experimental therapy may improve quality and extent of life. But in many cases, physicians must resist the urge to administer a relatively ineffective chemotherapy drug. A better choice is to discuss the likely results of such treatments and to set realistic goals with the patient. A patient's decision to forgo cancer treatment must be respected. Another alternative is the clinical trial, the risks and benefits of which deserve discussion.

Regardless of prognosis, quality of life in cancer patients may improve with nutritional support, effective pain management, other symptomatic palliative care, and psychiatric and social support of the patient and family. Above all, patients must know that the clinical team will remain involved and accessible for supportive care, regardless of the prognosis. Hospice or other related end-of-life care programs are important parts of cancer treatment. For more information pertaining to patients with incurable disease, see Ch. 353.