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Hematologic/Oncologic Disorders

1 Abetalipoproteinemia

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DEFINITION: Abetalipoproteinemia is an autosomal-recessive disorder characterized by the absence of apolipoprotein B (apoB)-containing lipoproteins in the plasma.

SYNONYMS: Low-density β -lipoprotein deficiency; Bassen-Kornzweig syndrome.

DIFFERENTIAL DIAGNOSIS: Hypobetalipoproteinemia; Chylomicron retention disease; Celiac disease.

SYMPTOMS AND SIGNS: Infants usually present with diarrhea, vomiting, and abdominal swelling. The disease is usually misdiagnosed as celiac disease, which has similar symptoms. Steatorrhea and poor weight gain are observed in infancy due to fat malabsorption. Plasma lipid levels are very low. Patients have mild to moderate anemia, usually with mild hemolysis. Plasma levels of lipid-soluble vitamins also are extremely low. During the first 10–20 years of life, the vitamin E deficiency results in neurologic complications such as loss of deep-tendon reflexes, and cerebellar signs such as dysmetria, ataxia, and spastic gait. By the third or fourth decade, untreated patients show severe ataxia and spasticity. These severe effects on the central nervous system are the ultimate cause of death in most patients, which often occurs by the fifth decade. Vitamin A deficiency results in a progressive pigmented retinopathy, characterized as an atypical retinitis pigmentosa. The first ophthalmic symptoms are decreased night and color vision. The retinitis pigmentosa usually begins at about age 10. In untreated patients, daytime visual acuity usually deteriorates to virtual blindness by the fourth decade. Vitamin K levels are also low and cause elevated prothrombin time and delayed coagulation.

ETIOLOGY/EPIDEMIOLOGY: Abetalipoproteinemia is an autosomal-recessive disease caused by mutations in the gene encoding for the 97-kDa subunit of microsomal triglyceride transfer protein (MTP). Mutations result in loss of *in vitro* lipid transfer activity in the liver and intestinal microsomes. The lack of MTP activity leads to the absence of apoB in plasma because apoB is not properly lipi-

dated and undergoes rapid presecretory degradation. To date, approximately 100 isolated cases from many parts of the world have been reported with a sex ratio of 1:1. Approximately one third of reported cases were due to consanguineous marriages.

DIAGNOSIS: Diagnosis is based on the measurement of lipid and apoB levels in the plasma, determination of red blood cell morphology, and eye examination. Lipid levels are extremely low. ApoB-containing lipoproteins (chylomicrons, very low density lipoproteins, and low-density lipoproteins) are not detectable in plasma. Acanthocytosis of red blood cells is also a diagnostic feature of the disease. Signs of fat-soluble vitamin deficiency such as retinitis pigmentosa are common.

TREATMENT

Standard Therapies: The symptoms of fat malabsorption can be largely eliminated by avoiding fat, particularly long-chain saturated fatty acids, in the diet. A lipid-poor diet permits normal absorption of carbohydrates and proteins and eliminates digestive intolerance. Administration of pharmacologic doses of fat-soluble vitamins is helpful: oral administration of 5–10 mg/day of vitamin K can normalize the prothrombin time. Plasma levels of vitamin A can be increased to the normal range by supplementing 25,000 IU daily or every other day. Vitamin E deficiency can be corrected by feeding 150–200 mg/kg per day of vitamin E.

Investigational Therapies: Gene therapy is being explored.

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2 Adenoid Cystic Carcinoma

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DEFINITION: Adenoid cystic carcinoma (ACC) is an uncommon form of malignant neoplasm that arises within secretory glands, most commonly the major and minor salivary glands of the head and neck. Other possible sites of origin include the trachea, lacrimal gland, breast, skin, and vulva. This neoplasm is defined by its distinctive histologic appearance.

DIFFERENTIAL DIAGNOSIS: Benign mixed tumor; Mucoepidermoid carcinoma; Polymorphous low-grade adenocarcinoma; Basaloid squamous carcinoma.

SYMPTOMS AND SIGNS: Symptoms and signs depend largely on the site of origin of the tumor. Early lesions of the salivary glands manifest as painless masses of the mouth or face, usually growing slowly. Advanced tumors may manifest with pain and/or nerve paralysis, for this neoplasm has a propensity to invade peripheral nerves. Tumors of the lacrimal gland may manifest with proptosis and changes in vision. Adenoid cystic carcinoma arising in the tracheobronchial tree may manifest with respiratory symptoms, whereas tumors arising in the larynx may lead to changes in speech.

ETIOLOGY/EPIDEMIOLOGY: Most individuals are diagnosed with the disease in the fourth through sixth decades of life, but a wide age range has been reported, including pediatric cases. The female:male ratio is approximately 3:2. No strong genetic or environmental risk factors have been identified. Damage to the DNA genome occurs in the development of ACC, as it does in all cancers studied to date. Various studies have shown chromosomal abnormalities and genetic deletions occurring in samples of ACC. Some evidence exists that the p53 tumor suppressor gene is inactivated in advanced and aggressive forms of this

neoplasm. Otherwise, the specific molecular abnormalities that underlie this disease process are unknown.

DIAGNOSIS: The diagnosis is made by histologic analysis of a biopsy or resection specimen of a tumor mass. The three major variant histologic growth patterns of ACC are cribriform, tubular, and solid. The solid pattern is associated with a more aggressive disease course. No serum markers exist for this neoplasm. Recurrences are usually identified by radiographic imaging techniques, such as CT.

TREATMENT

Standard Therapies: Surgical resection, whenever possible, is the mainstay therapy. Many centers advocate post-operative radiotherapy to help limit local failure. A few specialized centers offer neutron beam therapy, which may be more effective. No chemotherapy is effective for metastatic and/or unresectable ACC, although some patients may receive palliation.

Investigational Therapies: The effects of relatively new chemotherapeutic drugs (paclitaxel, gemcitabine), alone or in combination with other drugs, in the control of metastatic or locally recurrent ACC are being studied.

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3 Congenital Afibrinogenemia

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DEFINITION: Congenital afibrinogenemia, the most severe form of fibrinogen deficiency, is characterized by the complete absence of fibrinogen.

DIFFERENTIAL DIAGNOSIS: Hypofibrinogenemia; Dysfibrinogenemia; Hypodysfibrinogenemia.

SYMPTOMS AND SIGNS: Umbilical cord hemorrhage is often the first sign of the disorder; gum bleeding, epistaxis,

menorrhagia, gastrointestinal bleeding, and hemarthrosis occur with varying intensity, and spontaneous intracerebral bleeding and splenic rupture can occur as well.

ETIOLOGY/EPIDEMIOLOGY: Congenital afibrinogenemia is inherited in an autosomal-recessive manner and has an estimated prevalence of approximately 1 to 2 in 1 million. As with other autosomal-recessive diseases, the condition is clinically significant only when two alleles are mutated, in homozygosity or compound heterozygosity; both sexes are affected. The disease is caused by mutations in either of the three fibrinogen genes, *FGG*, *FGA*, or *FGB*, clustered on the long arm of human chromosome 4 (region 4q28-31). Many families with this disorder have been studied, allowing the identification of numerous causative mutations; researchers have found that most cases are due to null mutations in the *FGA* gene (>80% of patients studied).

DIAGNOSIS: The diagnosis is made following measurement of fibrinogen levels in patient plasma using standard laboratory analyses such as Clauss (clottable fibrinogen) and radial immunodiffusion, rocket immunoelectrophoresis, and nephelometry. Because the disease locus is known,

precise molecular diagnosis at the DNA level can be made, as can prenatal diagnosis.

TREATMENT

Standard Therapies: Treatment consists of plasma-derived fibrinogen preparations administered either prophylactically (every 2–4 weeks) or on demand, e.g., after trauma or before surgery.

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4 X-Linked Agammaglobulinemia

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DEFINITION: X-linked agammaglobulinemia is a chromosomal disorder restricted to B lymphocytes, characterized by recurrent sinopulmonary and gastrointestinal infections within the first 2 years of life.

SYNONYM: Bruton agammaglobulinemia.

DIFFERENTIAL DIAGNOSIS: AIDS; Hyper-IgM syndrome; CVID.

SYMPTOMS AND SIGNS: Children with X-linked agammaglobulinemia typically present within the first year of life with respiratory tract infections caused by encapsulated pyogenic bacteria, e.g., *Streptococcus pneumoniae* and *Haemophilus influenzae*. Gastrointestinal infections are also common. These infections are persistent despite appropriate therapy, occur in multiple locations, and are un-

usually severe. Skin infections (pyoderma) and systemic infections (sepsis, meningitis, septic arthritis) are less common. Complications are not associated with viral infections except with enteroviral infections, which may cause chronic meningoencephalitis, dermatomyositis-like syndrome, or hepatitis. Occasionally, patients may have septic arthritis or chronic arthritis. No striking characteristics are apparent on physical examination except for the paucity of lymphoid tissue, i.e., markedly hypoplastic tonsils and lymph nodes.

ETIOLOGY/EPIDEMIOLOGY: Mutations of the B cell-specific tyrosine kinase *Btk* gene, located on the long arm of X chromosome at Xq22, result in developmental arrest of B-cell maturation and function. Only males are affected and more than 1,000 cases have been reported or are known to exist. Carrier detection is available.

DIAGNOSIS: Quantitative immunoglobulin levels (IgG, IgM, IgA) are markedly decreased. IgG levels are typically below 100 mg/dL, but rarely may be as high as 300 mg/dL.

Characteristically, there is a failure to produce functional antibodies. Natural antibodies such as isohemagglutinins are reduced or absent, as are antibody responses to childhood vaccines such as tetanus, diphtheria, *H. influenzae* type B, or *Pneumococcus*. B-lymphocytes and plasma cells are absent in peripheral blood and tissues. Lymphocyte subsets as determined by monoclonal antibody staining (anti-CD19, anti-CD20) are diminished. *Btk* gene analysis is diagnostic. The latter two tests may also be used in the neonatal period or in the months shortly thereafter for diagnosis at a time when maternally acquired antibodies may obscure immunoglobulin levels.

TREATMENT

Standard Therapies: Replacement of immunoglobulin is mandatory. Immune globulin is given intravenously or, less commonly, by slow, subcutaneous infusion. Intramuscular gammaglobulin is rarely used because of the difficulty in achieving high serum IgG levels and the discomfort associated with it. Appropriate institution of antibiotics is im-

portant and prevents complications. Live viral vaccines (especially polio vaccine) are contraindicated.

Investigational Therapies: Various pharmaceutical companies are conducting B-cell growth or activation studies.

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5 Acquired Agranulocytosis

Yoriko Saito, MD

DEFINITION: Acquired agranulocytosis encompasses a large group of acquired conditions characterized by a decreased peripheral granulocyte count with an absolute neutrophil count (ANC) of less than 1,500/mm³.

SYNONYM: Acquired or secondary neutropenia.

DIFFERENTIAL DIAGNOSIS: Aplastic anemia; Hypocellular form of myelodysplastic syndrome; Preleukemia/leukemia; Fanconi anemia; Paroxysmal nocturnal hemoglobinuria; Ethnic/benign familial neutropenia; Kostmann syndrome/infantile agranulocytosis; Myelokathexis/neutropenia with tetraploid nuclei; Cyclic neutropenia; Schwachman-Diamond-Oski syndrome; Chediak-Higashi syndrome; Reticular dysgenesis; Dyskeratosis congenital.

SYMPTOMS AND SIGNS: The range of presentation is varied, from patients who are completely asymptomatic to patients who have recurrent and severe systemic infections. Patients with neutropenia associated with marrow failure or exhaustion caused by bone marrow transplantation, cancer chemotherapy, or other medications, and with pure

white cell aplasia, are at high risk for overwhelming bacterial sepsis. The types of infections in neutropenic patients depend on the degree and chronicity of the neutropenia as well as the nature of the associated diseases. Patients receiving suppressive chemotherapy are particularly at risk for bacterial sepsis and fungal infections. Viral and parasitic infections are less commonly found unless dysfunction of cell-mediated immunity is coexistent, such as in AIDS. Patients with less severe chronic neutropenia may present with recurrent sinusitis, stomatitis, perirectal infection, or gingivitis, usually without systemic septic manifestations.

ETIOLOGY/EPIDEMIOLOGY: Acquired agranulocytosis can present in any age group and in both sexes (Table 9.1). The overall annual risk for agranulocytosis is 3.4 per 1 million in an ambulatory population from Israel, Europe, and the northeast United States, with approximately 72% of all cases in the United States attributed to medications (Table 9.2).

DIAGNOSIS: In an asymptomatic patient, close observation for several weeks is appropriate, particularly in young children, where the most common neutropenias are benign. A detailed history of medication use must be taken.

TABLE 9.1 Etiologies of Acquired Agranulocytosis

Peripheral destruction of neutrophils	<ul style="list-style-type: none"> ■ Autoimmune neutropenia associated with systemic lupus erythematosus, rheumatoid arthritis/Felty, Sjögren, Graves, lymphoproliferative disease ■ Cold antibodies (infectious mononucleosis, <i>M. pneumoniae</i>) ■ Isoimmune neonatal neutropenia ■ Chronic benign neutropenia and chronic benign neutropenia of infancy and childhood (immune-mediated)
Bone marrow suppression/ineffective hematopoiesis	<ul style="list-style-type: none"> ■ Nutritional deficiency (folate, B₁₂, copper) ■ Pure white cell aplasia associated with thymoma ■ Neutropenia in infants of hypertensive mothers
Peripheral margination of neutrophils	<ul style="list-style-type: none"> ■ Neutrophil activation by means of complement in hemodialysis, membrane oxygenators, burns, transfusion-related acute lung injury (TRALI)
Multifactorial	<ul style="list-style-type: none"> ■ Drug-induced ■ Associated with viral (varicella, measles, rubella, hepatitis A/B, infectious mononucleosis, influenza, cytomegalovirus, parvovirus B19, Kawasaki), bacterial and other infections (<i>S. aureus</i>, brucellosis, rickettsia, <i>M. tuberculosis</i>) ■ Systemic sepsis ■ HIV/AIDS ■ Bone marrow transplantation ■ Graft-versus-host disease

The presence of recurrent infections suggests more significant neutropenia and may warrant a bone marrow examination. If neutropenia is persistent after several weeks of observation, a search for underlying disorders such as autoimmune diseases or lymphoproliferative disease may be considered.

TREATMENT

Standard Therapies: The major goal of therapy is the management of infectious complications (empiric broad-

coverage antibiotics for patients with chemotherapy or other drug-induced or severe infection-associated neutropenia, and management of recurrent nonsystemic infections in less severe chronic neutropenia). All patients with chronic neutropenia should receive routine preventive dental care. Corticosteroids and intravenous IgG have been effective in some cases of immune-mediated neutropenia. Recombinant granulocyte colony-stimulating factor has been shown to correct neutropenia in cyclic neutropenia, severe infantile agranulocytosis, and AIDS-associated neu-

TABLE 9.2 Medications Implicated in Acquired Agranulocytosis

<ul style="list-style-type: none"> ■ Marrow-suppressive chemotherapeutic agents ■ Dipyrrone ■ Mianserin ■ Sulfasalazine ■ Cotrimoxazole ■ Antiarrhythmic agents (procainamide, tocainamide, amiodarone, aprindine) ■ Digoxin ■ Dipyridamole ■ Propranolol ■ Benzodiazepines ■ Barbiturates ■ Gold compounds ■ Penicillins (amoxycillin, benzylpenicillin, azlocillin, phenethicillin, cloxacillin) 	<ul style="list-style-type: none"> ■ Thiouracil derivatives (methylothiouracil, propylthiouracil) ■ Phenylbutazone ■ Cimetidine, ranitidine ■ Penicillamine ■ Diclofenac ■ Carbamazepine ■ Angiotensin-converting enzyme inhibitors (captopril, enalapril) ■ Hydrochlorothiazide with potassium-sparing diuretic ■ Indomethacin ■ Cephalosporins (cephalexin, cephazolin, cefuroxime, cefitaxime, cephadrine) ■ Oxyphenbutazone ■ Nitrofurantoin ■ Salicylic acid derivatives 	<ul style="list-style-type: none"> ■ Clozapine ■ Carbimazole ■ Sulfonylurea derivatives (tolbutamide, glibenclamide) ■ Methyldopa ■ Thiamazole ■ Aminoglutethimide ■ Ibuprofen ■ Pentazocine ■ Levamisole ■ Promethazine ■ Chloramphenicol ■ Paracetamol and combination preparations ■ Perazine ■ Mebhydrolin ■ Imipramine
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tropenia. Granulocyte transfusions may be used in neutropenic patients with life-threatening bacterial and fungal infections after a trial of conventional therapies. Although the definitive therapy for drug-induced neutropenia is the withdrawal of the offending drug, this is not always practical. When there is no therapeutic alternative, a patient without infectious complications and ANC greater than 500–700/mm³ may be maintained on the putative causative medication with close observation.

Investigational Therapies: Several cytokines and chemokines are being explored.

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6 Ameloblastoma

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DEFINITION: Ameloblastomas are tumors that are derived from odontogenic epithelium. They are primarily found in the jawbones but, in rare (1%) cases, they can be found peripherally. Those located in the jawbones can be unicystic but more commonly are solid or multicystic. The unicystic lesions are seen in a younger age group, with most appearing within the first two decades of life. The more common multicystic ameloblastoma occurs in a wider range of ages.

DIFFERENTIAL DIAGNOSIS: Myxomas; Keratocysts; Hemangiomas; Aneurysmal bone cysts; Giant cell lesions, calcifying; Epithelial odontogenic tumors; Ameloblastic fibromas.

SYMPTOMS AND SIGNS: The clinical findings are non-specific. The patient may present with swelling. Rarely, there may be nasal obstruction with tumors involving the maxilla. Pain and neurologic changes would be atypical findings. Ameloblastomas are slow growing and locally invasive. Often, they are present as fortuitous findings on routine dental examinations and/or radiographs; however, sometimes they are missed or neglected and the patient presents later with massive swelling. Radiographically, ameloblastomas can be seen as unilocular and, more often, multilocular radioluscencies. The latter is often described as having a “soap bubble” appearance. Roots of adjacent teeth may be resorbed and the borders of the lesion can be irregular.

ETIOLOGY/EPIDEMIOLOGY: Ameloblastoma has no gender or ethnic predilection. The cells may be derived from the dental lamina, lining of odontogenic cysts, cell rests of the enamel organ, or from oral mucosal basal cells. No genetic or environmental influences on the development of these lesions are known.

DIAGNOSIS: Diagnosis is made by biopsy and histologic evaluation of the suspected lesion. CT scans are helpful in delineating the size and location of the tumor and in treatment planning.

TREATMENT

Standard Therapies: Treatment is surgical. The procedure depends on whether the lesion is unicystic or multicystic. The rarer unicystic ameloblastoma has a much lower recurrence rate compared with the multicystic form and can be treated by enucleation (removal of tumor) followed by curettage of surrounding bone. Multicystic lesions have a much higher recurrence rate and may require more aggressive excisions. Other factors that impact on surgical planning include anatomic location, patient age, and degree of cortical bone loss. The inferior border of the mandible should be preserved if at all possible. Children who will have adequate follow-up may be treated less aggressively. Lesions of the posterior maxilla and mandible should be treated more radically because recurrence into the adjacent soft tissue in these regions makes definitive therapy of the recurrence a challenge. In general, multicystic ameloblastomas are resected with wide margins, giving consideration to the patient's age and potential resulting deformity. Chemotherapy and radiation therapies have little role in the management of ameloblastomas. Reconstruction (particularly of larger mandibular defects) can be done with

bone grafts. Some surgeons may elect to do this at the time of resection.

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7 Acquired Aplastic Anemia

Neal Young, MD

DEFINITION: Acquired aplastic anemia is a bone marrow failure syndrome defined by pancytopenia with a very fatty, even empty, bone marrow.

DIFFERENTIAL DIAGNOSIS: Fanconi anemia (constitutional aplastic anemia); Myelodysplasia; Rare variants of leukemia; Myelofibrosis.

SYMPTOMS AND SIGNS: Symptoms are due to anemia, leukopenia, and thrombocytopenia. Most patients present with complaints secondary to bleeding or oxygen deprivation. Thrombocytopenia typically results in mucocutaneous hemorrhage manifested as petechiae, epistaxis, gingival oozing, and menorrhagia. Cardiovascular symptoms may predominate in the older, severely anemic patient, but more frequent are fatigue, lassitude, and shortness of breath. Infection is rare, but serious bacterial infections and ultimately progressive fungal disease are the most serious complications of pancytopenia. Physical examination is remarkable only for ecchymoses, petechiae, and pallor. Lymphadenopathy and splenomegaly are not present.

ETIOLOGY/EPIDEMIOLOGY: Most patients are older children, adolescents, or young adults. There is no gender preference. Aplastic anemia has an incidence of 2 in 1 million in Europe and Israel, but the rate is two- to threefold higher in Asia and probably other parts of the developing world, for reasons that are unclear.

DIAGNOSIS: Pancytopenia in an otherwise healthy young person suggests aplastic anemia. A bone marrow

biopsy is required to establish acellularity; leukemia and other invasive processes can be excluded on the aspirate smear. The prognosis is determined quantitatively by the degree of pancytopenia; patients with <200 neutrophils/mL have an especially poor prognosis.

TREATMENT

Standard Therapies: Most aplastic anemia probably results from immunologic (autoimmune) destruction of hematopoietic cells by T-lymphocytes. Effective therapy is provided either by hematopoietic stem cell transplantation or immunosuppression. Bone marrow transplantation from a histocompatible sibling is the treatment of choice in children and younger patients, especially if neutropenia is severe. For most other patients, immunosuppression and bone marrow transplantation provide roughly equivalent outcomes. Immunosuppression is usually a combination of antithymocyte globulin with cyclosporine. The 5-year survival rate for severe aplastic anemia treated with either stem transplantation or immunosuppression is 70%–80%. In aplastic anemia, hematopoietic growth factors or corticosteroids are not indicated and may be dangerous. Transfusion therapy and the treatment of severe infections is best managed by hematology or oncology specialists.

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8 Diamond-Blackfan Anemia

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DEFINITION: Diamond-Blackfan anemia (DBA) is congenital pure red cell aplasia.

SYNONYMS: Blackfan-Diamond anemia; Congenital hypoplastic anemia; Chronic congenital aregenerative anemia; Hereditary red cell aplasia; Congenital erythroid hypoplasia; Erythrocytogenesis imperfecta; Chronic idiopathic erythroblastopenia with aplastic anemia (type Josephs-Diamond-Blackfan); Aase syndrome.

DIFFERENTIAL DIAGNOSIS: Acquired pure red cell aplasia; Transient erythroblastopenia of childhood (TEC); Parvovirus B19 infection; Fanconi anemia; Aplastic anemia; Autoimmune hemolytic anemia.

SYMPTOMS AND SIGNS: Pallor, lassitude, and even congestive heart failure may occur, due to severe anemia. Approximately 30% of patients are diagnosed in the first 3 months of life, 90% in the first year. One third have physical anomalies, such as abnormal thumbs, characteristic facies, or short neck; short stature is common. A substantial risk exists for the development of myelodysplastic syndrome or acute myeloid leukemia, as well as selected solid tumors such as osteosarcomas.

ETIOLOGY/EPIDEMIOLOGY: There are at least three different gene loci for DBA. Approximately 20% have mutations at 19q13 in RPS19, which are inherited in an autosomal dominant manner. The molecular mechanism is not known. Males and females are affected equally, and all racial and ethnic groups have been reported. Diamond-Blackfan anemia is estimated to occur in 5 to 10 per 1 million live births.

DIAGNOSIS: Patients with DBA have a macrocytic anemia, with reticulocytopenia and marrow erythroblastopenia. White blood cells and platelets are usually normal. Bone marrow examination distinguishes the red

cell underproduction in this condition from erythroid hyperplasia in hemolytic anemias. Erythroid vacuoles and nuclear inclusions suggest parvovirus. Red cell adenosine deaminase is elevated in most patients.

TREATMENT

Standard Therapies: More than half of patients respond to treatment with prednisone. Patients who do not respond to steroids can be transfused with leukocyte-depleted, irradiated, packed red blood cells. Iron overload requires chelation with parenteral desferrioxamine. Remissions occur in approximately 25% of patients, both prednisone-responsive and those solely transfused. Stem cell transplant (with bone marrow or cord blood) is an option for patients with an HLA-matched sibling donor.

Investigational Therapies: Researchers are investigating stem cell transplant for DBA from alternative donors.

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9 Fanconi Anemia

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DEFINITION: Fanconi anemia (FA) is an inherited autosomal-recessive disorder with a high frequency of aplastic anemia, often associated with characteristic birth defects.

SYNONYMS: Estren-Dameshek anemia; Constitutional aplastic anemia type I and II; Fanconi pancytopenia; Aplastic anemia with congenital anomalies; Congenital pancytopenia.

DIFFERENTIAL DIAGNOSIS: Acquired aplastic anemia; Dyskeratosis congenital; Amegakaryocytic thrombocytopenia; Thrombocytopenia absent radii; Bloom syndrome; Seckel syndrome; Dubowitz syndrome.

SIGNS AND SYMPTOMS: Bruising, pallor, or infection may be the first signs of bone marrow failure. Hematologic changes such as thrombocytopenia, followed by macrocytic anemia and neutropenia, occur at a median age of 6.5 years in males and 8 years in females. Approximately 75% of patients with FA have birth defects, including short stature, café-au-lait spots and hyper- or hypopigmentation, abnormal thumbs and radial rays, structural renal anomalies, microcephaly, microphthalmia, hearing defects, and others. There is a high risk of development of myelodysplastic syndrome and acute myeloid leukemia, as well as specific solid tumors (particularly oropharyngeal, esophageal, vulvar cervical, and liver neoplasias).

ETIOLOGY/EPIDEMIOLOGY: Inheritance is autosomal recessive. At least seven complementation groups have been identified, with six genes mapped and cloned. Affected patients are homozygotes or double heterozygotes for mutations of FA genes in the same complementation group. The heterozygote frequency ranges from approximately 1 in 100 to 1 in 300, depending on the population, with the expected number of new cases estimated to be 1 in 40,000 to 1 in 360,000 live births. The male:female ratio is 1.2:1 in the more than 1,000 cases reported in the literature. All racial and ethnic groups have been reported.

DIAGNOSIS: Cytopenias in a child with characteristic morphologic abnormalities strongly suggest the diagnosis, but patients with FA are definitively diagnosed by the presence of increased chromosome breaks and rearrangements in peripheral blood T-lymphocytes cultured with DNA cross-linking agents such as diepoxybutane or mitomycin C (MMC), and/or by increased numbers of cells arrested in cell cycle at G2/M. Genotyping may be done with retroviral

transduction of cells with candidate genes, with the end point of the assay being correction of sensitivity to MMC. Within complementation groups, common mutations are investigated first, followed by complete sequencing as needed. Complete assessment of the hematologic status requires blood counts, bone marrow examinations, and marrow cytogenetics.

TREATMENT

Standard Therapies: The management of FA requires a multidisciplinary team of subspecialists, including hand surgeons, nephrologists, urologists, gastroenterologists, and endocrinologists. Treatment is indicated when the patient's platelet count is $<30,000/\text{mm}^3$, hemoglobin $<8 \text{ g/dL}$, and/or neutrophils $<500/\text{mm}^3$. Hematopoietic stem cell (bone marrow, cord blood, or peripheral blood) transplantation is recommended if there is an HLA-matched sibling donor. Medical treatment of anemia (with some effect on platelets) consists of androgens (usually oxymetholone) with or without prednisone, and/or granulocyte colony-stimulating factor specifically for neutropenia. Supportive care includes transfusion of leukocyte-depleted, irradiated, packed red blood cells or platelets and antibiotics. Hand surgery can be performed to correct thumb abnormalities.

Investigational Therapies: Alternative donor transplantation is high risk and reserved for patients with acute leukemia, clinical myelodysplastic syndrome, or refractory aplastic anemia. Improved stem cell transplantations are being evaluated, and gene therapy trials are being developed. Researchers are also studying genotype/phenotype and predictors of leukemia and solid tumors.

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10 Autoimmune Hemolytic Anemias

Lawrence D. Petz, MD

DEFINITION: Autoimmune hemolytic anemias (AIHA) are a group of disorders characterized by anemia resulting from a shortened red blood cell lifespan that is caused by autoantibodies. Autoimmune hemolytic anemias are divided into three categories depending on the characteristics of the autoantibodies: warm antibody AIHA, cold agglutinin syndrome, and paroxysmal cold hemoglobinuria.

DIFFERENTIAL DIAGNOSIS: Iron deficiency anemia; Aplastic anemia; Anemia of chronic disease; Megaloblastic anemia; Anemia associated with marrow infiltration; Thalassemia; Hemoglobinopathies; Enzyme deficiencies; Paroxysmal nocturnal hemoglobinuria; Microangiopathic hemolytic anemia.

SYMPTOMS AND SIGNS: Individuals with anemia of any cause may have fatigue, shortness of breath, and palpitations. Clinical manifestations of hemolytic anemia are pallor, jaundice, and splenomegaly. In individuals with mild anemia, these findings may be absent and, in such cases, diagnosis is dependent on laboratory findings.

ETIOLOGY/EPIDEMIOLOGY: Autoimmune hemolytic anemia is likely caused by a breakdown in the mechanisms that normally prevent an individual from forming antibodies against his or her own normal tissues. How this happens is unknown, and probably varies among the various types of AIHA. The prevalence of AIHA of all categories is about 1 in 25,000 individuals overall, and 1 in 41,000 for the warm antibody type. There is a general increase in incidence throughout life, with a significant rise occurring in individuals older than 50 years. The disorder is more common in females, with a male:female ratio of about 1:1.3.

DIAGNOSIS: The patient's history and physical examination may suggest a hemolytic anemia, but usually the manifestations are nonspecific and the diagnostic workup involves a laboratory evaluation of anemia. Laboratory indications of hemolysis are sought by tests that yield evidence of increased hemoglobin breakdown and of bone marrow regeneration. A positive direct antiglobulin test indicates that the hemolysis is caused by autoantibodies. Determining the characteristics of antibodies in the patient's

serum by specialized laboratories distinguishes between warm antibody AIHA, cold agglutinin syndrome, and paroxysmal cold hemoglobinuria.

TREATMENT

Standard Therapies: The initial therapy for patients with autoimmune hemolytic anemia of warm antibody type should be corticosteroids. If remission cannot be maintained on low doses, alternative treatment is indicated because of the side effects of long-term corticosteroid treatment. Splenectomy should be considered in patients who do not respond to corticosteroids because it has the potential for complete and long-term remission. A syndrome of overwhelming postsplenectomy infection (OPSI) may occur, however, which has high morbidity and mortality. Other therapies that have been used with modest success are high-dose intravenous immunoglobulin, plasma exchange, danazol, and immunosuppressive drugs such as azathioprine, cyclophosphamide, and cyclosporine. Therapy for cold agglutinin disease is generally less effective and consists of avoidance of exposure to severe cold and the use of chlorambucil. Corticosteroids and splenectomy are not as commonly effective as they are in warm antibody AIHA. Plasma exchange offers a modest degree of temporary benefit in some patients with cold agglutinin syndrome. Paroxysmal cold hemoglobinuria generally subsides spontaneously, but is often treated with corticosteroids during an acute hemolytic episode. Transfusions should be provided for all patients when necessary. Transfused red blood cells generally survive as well as the patient's own and provide temporary benefit while other therapy is taking effect.

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11 Cold Hemolytic Anemia Syndromes

Kenneth M. Algazy, MD

DEFINITION: Cold hemolytic anemia syndromes are autoimmune disorders caused by antibodies that bind to red blood cells (RBCs) at temperatures less than 37°C. The two major types are based on the type of antibody present: agglutinins and hemolysins (Donath-Landsteiner antibody). Acute cold agglutinin syndrome is more common and accounts for approximately one third of all autoimmune hemolytic anemias. The syndrome of paroxysmal cold hemoglobinuria (PNH) due to hemolysins is rare. Hemolysis from cold-reacting antibodies occurs less commonly than warm antibody-induced hemolysis, but a greater possibility exists of precipitating complement activation, which can induce intravascular red cell destruction.

SYNONYMS: Cold agglutinin disease; Cryopathic hemolytic syndromes.

DIFFERENTIAL DIAGNOSIS: Warm autoimmune hemolytic anemias; Hereditary hemolytic anemias; Paroxysmal nocturnal hemoglobinuria; Hemoglobinopathy-associated hemolytic anemias.

SYMPTOMS AND SIGNS: The patient presents with chronic hemolysis, with or without jaundice, or episodes of acute fulminant hemolysis induced by a decrease in body temperature. The presence of cold-reacting hemolysis should be suspected if the patient develops acrocyanosis, skin necrosis (rare), hemolysis, or simply anemia during recovery from an infection. Numbness or occasionally pain may accompany the color changes (Raynaud phenomena), and, rarely, trophic changes and even gangrene of extremities have been reported. Splenomegaly may be present depending on the etiology. Laboratory findings demonstrate anemia, evidence of reticulocytosis, mild indirect hyperbilirubinemia (less than 3.5 mg/dL), hemoglobinemia if intravascular hemolysis, low or absent haptoglobin levels, and chronic low-grade hemoglobinuria and hemosiderinuria. The cold agglutinin titer may range from 1:1,000 to 1:1,000,000, usually in the range of 1:25,000; the blood bank can demonstrate greater reactivity in the cold. The direct antiglobulin test result will be

positive; sometimes, normal donor type-specific RBCs will react more vigorously with the patient's serum because the patient's RBC receptors are already tightly bound with antibody.

ETIOLOGY/EPIDEMIOLOGY: Chronic idiopathic cold agglutinin disease occurs primarily in the elderly, with a peak incidence in the seventh and eighth decades of life. Occasionally, younger adults and even children can develop cold agglutinins. Most cold agglutinins can be identified in the blood bank as IgM with either big I or little i antigen specificity. Malignant clones of lymphoid cells (lymphomatous malignancy) or simply antigenically stimulated B-lymphocytes produce the antibodies. Infectious agents can complex with I/i antigens to cause antibody production. These disorders can also appear as a cold agglutinin disease due to a monoclonal proliferation of B cells or can appear as paroxysmal cold hemoglobinuria secondary to certain viruses in children or syphilis (congenital or tertiary).

TREATMENT

Standard Therapies: Because the antibodies react preferentially in the cold, the hallmark of therapy is to keep the patient warm. Transfusion with cross-matched RBCs should be undertaken only if the patient develops severe anemia and/or the threat of cardiovascular compromise. Neither splenectomy nor the use of steroids is effective therapy for chronic cold agglutinin disease. For severe chronic hemolysis secondary to cold agglutinin disease, chlorambucil or cyclophosphamide has been used to decrease antibody production. In dire circumstances, plasma exchange can be used to remove the offending antibody, as long as the blood as well as the patient can be maintained at 37°C. Treatment with interferon- α may also be useful.

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12 Congenital Nonspherocytic Hemolytic Anemia

Pamela S. Becker, MD, PhD

DEFINITION: Congenital nonspherocytic hemolytic anemia is a group of inherited hemolytic anemias characterized by early destruction of red blood cells in the circulation due to defects in the red cell enzymes. Of the several types of enzyme deficiencies, the most common is glucose-6-phosphate dehydrogenase (G6PD) deficiency.

SYNONYMS: Congenital hemolytic anemia; Glucose 6-phosphate dehydrogenase deficiency; Pyruvate kinase (PK) deficiency.

DIFFERENTIAL DIAGNOSIS: Hexokinase deficiency; Glucosephosphate isomerase deficiency; Phosphofructose kinase deficiency; Aldolase deficiency; Triosephosphate isomerase deficiency; Pyrimidine nucleotidase deficiency; Adenosine deaminase excess; Glutathione synthetase deficiency; Glutathione reductase deficiency; Acquired hemolytic anemia.

SYMPTOMS AND SIGNS: Most patients with G6PD deficiency have anemia and symptoms only after exposure to certain oxidant drugs or chemicals, but some have variants that have ongoing chronic hemolysis. The other enzyme deficiencies are associated with variable degrees of chronic hemolytic anemia. Symptoms include pallor and fatigue. At times of infection or stress (e.g., pregnancy), the anemia can worsen and be accompanied by jaundice. Severely affected patients may have chronic jaundice. Other symptoms include neonatal jaundice, gallstones by the teenage years, and enlargement of the spleen. Some infections, such as one type of parvovirus, B19, can lead to aplastic crisis, characterized by lack of red cell production and, consequently, profound anemia for a period of approximately 10 days. Signs include pale conjunctivae, icteric sclerae, palpable splenomegaly, and gallstones seen on ultrasonographic examination.

ETIOLOGY/EPIDEMIOLOGY: G6PD deficiency is X-linked recessive, and PK deficiency is autosomal recessive. The pathogenesis of these forms of hemolytic anemia is related to enzyme deficiency related to defects in the glycolytic pathway, the pentose phosphate pathway, nucleotide, or glutathione metabolism. It is the most common disorder of red cell metabolism, affecting more than 200 million people worldwide. The incidence varies among dif-

ferent ethnic groups, affecting 12% of African American males, 35% of those living at low altitude in Sardinia, 20%–32% in lowland Greece, 14% in Cambodia, 5.5% in China, and 2.6% in India. Of the enzyme deficiencies in the glycolytic pathway, the most common is PK deficiency. PK deficiency occurs worldwide, with a prevalence for heterozygosity of approximately 1% in the United States. The gene for G6PD is located on the X chromosome, band Xp28, and the PK gene is located on chromosome 1q21.

DIAGNOSIS: Laboratory evaluation includes a complete blood count, peripheral blood smear, reticulocyte count, serum total and direct bilirubin, and lactate dehydrogenase (LDH). The hemoglobin and hematocrit values are mildly to moderately decreased. The peripheral blood smear may show specific features for certain enzyme deficiencies: for example, bite cells or blister cells for G6PD deficiency, and echinocytes for PK deficiency. The reticulocyte count and index are elevated, as are the indirect bilirubin and LDH. The specific enzyme assays are diagnostic for each disorder. Abdominal ultrasonography demonstrates the presence of gallstones and splenomegaly. After splenectomy, the reticulocyte count in patients with PK deficiency can rise as high as 40%–70%.

TREATMENT

Standard Therapies: The standard treatment is folic acid replacement, so that adequate stores will be available to maintain increased red cell production. Red cell transfusions may be needed for profound anemia during aplastic crisis, or on a chronic basis for the rare, severe forms. For severe neonatal jaundice, exchange transfusion may be required. Splenectomy can greatly ameliorate the symptoms of chronic hemolytic anemia. Cholecystectomy is often required to ameliorate symptoms related to gallstones. Patients with iron overload may also require treatment with chelating agents.

Investigational Therapies: Studies of gene transfer are currently under investigation.

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13 Hereditary Spherocytic Hemolytic Anemia (Hereditary Spherocytosis)

Pamela S. Becker, MD, PhD

DEFINITION: Hereditary spherocytosis (HS) is an inherited hemolytic anemia characterized by aberrant red cell shape. The cells are more susceptible to damage and have a short survival due to destruction, largely in the spleen.

SYNONYMS: Spherocytosis; Spherocytic hemolytic anemia.

DIFFERENTIAL DIAGNOSIS: Autoimmune hemolytic anemia; Hereditary stomatocytosis; ABO incompatibility in the neonate.

SYMPTOMS AND SIGNS: Symptoms include pallor and fatigue related to anemia. With infection or stress (e.g., pregnancy), the anemia can worsen and can be accompanied by jaundice. Other symptoms include neonatal jaundice, gallstones by the teenage years, and enlargement of the spleen. Some infections, such as one type of parvovirus, B19, can lead to aplastic crisis, characterized by lack of red cell production and, consequently, profound anemia for approximately 10 days, until the red cell production recovers. Signs include pale conjunctivae, icteric sclerae, palpable splenomegaly, and gallstones seen on ultrasonography. Severe forms can be associated with chronic jaundice and transfusion-dependent anemia.

ETIOLOGY/EPIDEMIOLOGY: The typical, common form is autosomal dominant, although there are rare occurrences of autosomal-recessive forms. Pathogenesis is based on red cell membrane loss, leading to reduced membrane surface area and, consequently, conversion of the classic biconcave shape to that of a sphere. Most cases of the autosomal-dominant form are due to ankyrin defects, including point mutations, truncations, and gene deletions. Ankyrin deficiency leads to loss of spectrin; therefore, HS usually has a combined ankyrin and spectrin deficiency. The gene for ankyrin is located on chromosome

8p11.2, for alpha spectrin on chromosome 1q22-q25, for beta spectrin on chromosome 14q23-q24.2, and for protein 4.2 on chromosome 15q15-q21. Autosomal-dominant HS is the most common hemolytic anemia in the Northern European population, with an incidence of approximately 1 in 5,000. It is less common in other races and ethnic groups.

DIAGNOSIS: Laboratory evaluation includes a complete blood count, peripheral blood smear, reticulocyte count, serum total and direct bilirubin, and lactate dehydrogenase (LDH). The hemoglobin and hematocrit values are mildly to moderately decreased, the mean corpuscular volume slightly decreased, and the mean corpuscular hemoglobin concentration slightly elevated. The peripheral blood smear shows variable spherocytes and microspherocytes, as well as polychromatophils and acanthocytes. In the autosomal-recessive form, poikilocytes and schistocytes may also be present. The reticulocyte count and index are elevated, as are the indirect bilirubin and LDH. The definitive assay for spherocytosis is the osmotic fragility test. The test does not distinguish autoimmune hemolytic anemia from hereditary spherocytosis, so a direct and indirect antiglobulin (Coombs) test is necessary to exclude autoimmune hemolytic anemia. Abdominal ultrasonography demonstrates the presence of gallstones and splenomegaly.

TREATMENT

Standard Therapies: The standard treatment is folic acid replacement, so that adequate stores will be available to maintain increased red cell production. Red cell transfusions may be needed for times of profound anemia during aplastic crisis, or on a chronic basis for the severe forms. For severe neonatal jaundice, exchange transfusion may be required. If patients have moderate to severe anemia and/or chronic jaundice, splenectomy will usually nearly eliminate the symptoms of the autosomal-dominant condition and improve the symptoms in the more severe recessive forms. Cholecystectomy is often required to ameliorate the symptoms related to the gallstones.

Investigational Therapies: Subtotal splenectomy and gene transfer are under investigation.

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14 Warm Antibody Hemolytic Anemia

Lawrence D. Petz, MD

DEFINITION: Warm-reactive autoimmune hemolytic anemia (AIHA) due to IgM antibodies is a form of autoimmune hemolytic anemia caused by IgM autoantibodies directed against red cell membrane antigens with maximal activity at 37 °C (warm-reactive).

SYNONYMS: Warm autoimmune hemolytic anemia secondary to IgM autoantibodies; Warm-reactive AIHA secondary to IgM.

DIFFERENTIAL DIAGNOSIS: Cold agglutinin disease or AIHA due to cold-reactive IgM; Autoimmune hemolytic anemia due to IgG; Hereditary spherocytosis; Clostridial sepsis; Early stages of Wilson disease; Hyperlipoproteinemic liver disease.

SYMPTOMS AND SIGNS: Patients present with pallor and anemia secondary to red blood cell hemolysis. Hemoglobinuria, hemoglobinemia, and occasionally icterus develop if hemolysis is brisk. Patients with high titer, complete warm-reactive AIHA from IgM antibodies have clinical features related to *in vivo* agglutination. Severe red blood cell agglutination can compromise perfusion diffusely and lead to infarction involving virtually any organ. For example, patients may have skin mottling, painful acrocyanosis, and skin necrosis that results from red cell agglutination in the cutaneous capillaries. Hemodynamic decompensation occurs with hemagglutination in the pulmonary vascular bed and heart. Symptoms may mimic a pulmonary embolism. Infarction and ultimately tissue necrosis may also involve the brain, kidney, or liver.

ETIOLOGY/EPIDEMIOLOGY: Autoimmune hemolytic anemia is caused by autoantibodies directed against red

blood cell membranes. In adults, AIHA is often associated with an underlying autoimmune disease, such as systemic lupus erythematosus. Most commonly, AIHA occurs in middle-aged and older individuals, with a peak incidence at 50 years. Most cases of AIHA can be separated into two groups based on thermal amplitude. The annual incidence of AIHA is estimated to be 1 in 80,000 persons, although most of these cases are IgG-mediated warm-reactive AIHA or, less commonly, IgM-mediated cold-reactive AIHA. In unusual cases, AIHA is caused by warm-reactive IgM autoantibodies.

DIAGNOSIS: For most cases of AIHA, the direct antiglobulin test or Coombs test is diagnostic, although the red cell agglutination in warm-reactive, IgM-mediated AIHA may preclude testing with the Coombs reagent. To define the antibody, further serologic studies are required. A reducing agent that inactivates IgM by breaking disulfide bonds but does not affect IgG antibodies, DTT, can be used to distinguish IgM from IgG antibodies. Radioimmune antiglobulin test can also be used to determine if antibody is bound to the red cell membrane. To define the red cell antigen recognized by the antibody, patient serum can be reacted with high-frequency, antigen-negative red cells. Thermal amplitude studies are used to define the optimal binding temperature of the antibody.

TREATMENT

Standard Therapies: Therapy has included supportive measures with packed red blood cell transfusions. If patients have hemodynamic instability and respiratory failure, pressor support and mechanical ventilation may be necessary. In an effort to limit the antibody, immunosuppressive therapies have been tried, including cytoxan, mycophenolate, and cyclosporine A. Red cell exchanges, plasmapheresis, and erythrocytapheresis have been used to remove circulating antibodies. Corticosteroid therapy is

typically initiated to decrease the antibody production. Although aggressive immunosuppressive therapy has been used, all previously reported cases of high-titer, complete, warm-reactive, IgM-mediated AIHA have been fatal.

Investigational Therapies: Treatment with Rituximab may be beneficial, but further studies are needed.

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15 Sickle Cell Anemia

Garrett E. Bergman, MD

DEFINITION: Sickle cell anemia is a severe chronic hemolytic anemia usually manifested in childhood, characterized by abnormally shaped red blood cells, reticulocytosis, and recurrent episodes of “crises” of pain, primarily in bone, muscle, or the abdomen.

DIFFERENTIAL DIAGNOSIS: Aplastic anemia; Thalassemia major; Other hemolytic anemias.

SYMPTOMS AND SIGNS: Infants, generally older than 3 months and toddlers may present with the unique hand-foot syndrome of sickle cell anemia: painful, generally symmetric swelling of the dorsum of the hands and/or feet, associated with a chronic hemolytic anemia. Growth retardation in early childhood is common. The initial presentation may be sudden and unexpected overwhelming sepsis, primarily from encapsulated organisms (*Haemophilus influenza* and *Streptococcus pneumoniae*). This catastrophic event is secondary to functional asplenia. Older children and adults have recurrent episodes of vasoocclusive or “painful crises” involving the muscles and bones of the arms, legs, abdomen, and back. Osteomyelitis also occurs more frequently in patients with sickle cell anemia. Children and adults may develop severe cerebrovascular strokes from occlusion of the major blood vessels in and around the brain. Hepatosplenomegaly may be seen early in life, but by age 5 or 6 years the spleen is not palpable. The acute chest syndrome, with severe chest pain and infiltrates on chest films, is believed to be due to combined infection and microinfarctions. Common complications include gallstones, aregenerative or aplastic crises, and iron overload.

ETIOLOGY/EPIDEMIOLOGY: A single genetic amino acid substitution of valine for glutamic acid at the number 6 position in the β chain of the hemoglobin molecule alters its intramolecular configuration and renders it susceptible to “sickling,” a form of protein denaturation. The abnormal hemoglobin is called sickle hemoglobin. Cells containing a high enough concentration of sickle hemoglobin can undergo internal polymerization, under certain conditions of deoxygenation, and deform the shape of the red cell. These sickled cells are much less flexible and unable to traverse the microvascular bed; they occlude small vessels through the body and cause acute painful local anoxia and chronic organ damage in virtually all organs. The gene is inherited in an autosomal-recessive manner, with males and females affected equally. The gene is a common mutant, prevalent in Central Africa, the Middle East, the Mediterranean, and in parts of India. African Americans have a gene incidence of approximately 8%, leading to an incidence of the homozygous disease state of approximately 1 in 580 newborns.

DIAGNOSIS: The diagnosis can be suspected in the presence of a chronic hemolytic anemia by the direct observation of sickle cells upon microscopic examination of the peripheral blood. Sickle hemoglobin-containing red blood cells can be induced to develop sickle forms in a simple test called a sickle cell preparation. Diagnosis is confirmed by hemoglobin electrophoresis.

TREATMENT

Standard Therapies: Aggressive general supportive therapy for any of the protean complications is mandatory. There is no curative therapy, and there is no proven medication that can decrease the symptoms or consequences of chronic disease. Patients should probably be treated with

supplemental oral folic acid to avoid an aregenerative crisis. Early in life, affected children should receive vaccinations for *H. influenza* and *S. pneumoniae* to diminish the risk of sudden overwhelming sepsis. Daily oral antibiotic prophylaxis (e.g., amoxicillin) against these organisms has been recommended until school age or even later. In only occasional and selected patients, or in all patients for certain serious complications such as strokes, a regimen of chronic red blood cell transfusion is indicated. Any chronic transfusion program must be coupled with an aggressive iron-chelation regimen to prevent iron overload–related multi-organ damage. Intermittent painful crises must be treated with adequate analgesic medications, including narcotics. Possible precipitating events should be sought and, if identified, treated aggressively. Patients will often need adequate and careful rehydration during any crisis. Oral administration of hydroxyurea has been useful in some cases to di-

minish the frequency of painful vasoocclusive episodes; the long-term value of this therapy is uncertain.

Investigational Therapies: Bone marrow transplantation is being explored.

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16 X-linked Sideroblastic Anemia

**Masayuki Yamamoto, MD, PhD,
and Hideo Harigae, MD, PhD**

DEFINITION: X-linked sideroblastic anemia (XLSA) is an inherited disease linked to a deficiency in erythroid-specific 5-aminolevulinate synthase (ALAS-E).

DIFFERENTIAL DIAGNOSIS: Idiopathic hemochromatosis; Pearson syndrome; Secondary drug-induced sideroblastic anemia; Primary acquired sideroblastic anemia; Autosomally inherited sideroblastic anemia; XLSA with cerebellar ataxia; Copper deficiency; Zinc overload.

SYMPTOMS AND SIGNS: Patients exhibit various grades of anemia. The severe form can be recognized in newborns and during infancy by symptoms of anemia, namely, pale skin and growth retardation. Patients with mild disease may reach adulthood without showing any symptoms of anemia. After middle age, patients exhibit symptoms of hemochromatosis, such as liver cirrhosis, glucose intolerance, renal failure, congestive heart failure, and arrhythmias.

ETIOLOGY AND EPIDEMIOLOGY: Associated with ALAS-E deficiency, XLSA is inherited in an X-chromosome linked fashion. Females are rarely affected. The disease is due to a mutation in the *ALAS-E* (*ALAS2*) gene, which is located on chromosome Xp11.21. No apparent deviation has been observed among ethnic groups.

DIAGNOSIS: The anemia is hypochromic and microcytic. In most carrier females, red cell histograms are biphasic. In severe cases, deformity of red cells is prominent, showing anisocytosis, poikilocytosis, and target cells. The levels of serum iron and ferritin are high, with an increased saturation level of transferrin. The cellular composition of bone marrow is sometimes hyperplastic, with the erythroid series being dominant. Ring sideroblasts are observed in more than 15% of nucleated cells. The activity of 5-aminolevulinate synthase in bone marrow is low, and the level of ALA is decreased. A definite diagnosis can be made based on the detection of a mutation in the coding region of the *ALAS-E* gene. Mutations are frequently detected in exons 5 and 9.

TREATMENT

Standard Therapies: Alterations in the ALAS-E protein structure, caused by mutation, can impair the binding ability of pyridoxal 5'-phosphate cofactor. Oral administration of pyridoxine may restore the activity and improve anemia. Patients who are refractory to pyridoxine treatment require blood transfusion as an alternative treatment. For mild cases, phlebotomy may be an effective remedy for depleting iron levels. For severe and rapidly progressing cases, stem cell transplantation should be encouraged.

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17 X-Linked Sideroblastic Anemia and Cerebellar Ataxia (XLSA/A)

**Roland Lill, MD,
and Gyula Kispal, MD**

DEFINITION: XLSA/A (OMIM 301 310) is a recessive disorder characterized by onset in infantile or early childhood of nonprogressive spinocerebellar ataxia and mild anemia with hypochromia and microcytosis. The disorder is associated with diminished tendon reflex, incoordination, elevated free erythrocyte protoporphyrin, normal parenchymal iron stores, and irresponsiveness to pyridoxine supplementation. These latter criteria and the neurologic symptoms distinguish the disorder from the more common X-linked sideroblastic anemia.

SYNONYMS: Sideroblastic anemia; Spinocerebellar ataxia.

DIFFERENTIAL DIAGNOSIS: X-linked sideroblastic anemia; Iron deficiency anemia.

SYMPTOMS AND SIGNS: Affected patients are born at low birth weight (~2.5 kg). Infants exhibit mild postnatal growth retardation and substantially impaired gross motor and cognitive development; however, patients are without sensory loss or mental retardation and exhibit normal intelligence. In some cases, affected family members show mild spasticity. Selective cerebellar hypoplasia is evident on CT. Patients are anemic with hypochromic (MCH) and microcytic (MCV) erythrocytes. Blood film examination shows Pappenheimer bodies. Red cell precursors contain sideroblasts, i.e., mitochondria with granular deposits of iron. Bone marrow examination reveals ring sideroblasts, indicating increased erythrocyte iron. Serum contains normal or only slightly elevated levels of ferritin, whereas soluble transferrin receptor (sTfR) concentrations are elevated significantly (30–50 µg/L). Total erythrocyte protoporphyrin is increased (20 µM). The normal synthesis of heme by incorporation of ferrous iron into protoporphyrin seems to be defective. This last step of heme biosynthesis is catalyzed by ferrochelatase in the mitochondrial matrix. The effect on heme biosynthesis is not directly linked to the function of protein mutated in XLSA/A, the mitochondrial ABC transporter ABC7.

ETIOLOGY/EPIDEMIOLOGY: XLSA/A is inherited in an X-linked recessive manner. The disease is due to mutations in the ABC transporter ABC7 (ABCB7 according to nomenclature by www.humanabc.org). The ABC7 gene is located on chromosome Xq13. The ABC7 protein is a constituent of the mitochondrial inner membrane and performs a crucial function in the export from mitochondria of an (unknown) component required for the maturation of cytosolic iron-sulfur (Fe-S) proteins, a process that is indispensable for a eukaryotic cell. The prevalence is not known because only a few cases have been examined.

DIAGNOSIS: The diagnosis is based on the presence of a mild anemia, which sometimes can be overlooked. The disorder is associated with spinocerebellar ataxia. Males with early-onset ataxia should receive a hematologic evaluation, including a blood film and serum iron status. A bone marrow examination should be performed, if abnormal blood count indices, increased concentrations of free erythrocyte protoporphyrin, and increased sTfR are detected. It reveals a large number of immature red cells with intramitochondrial iron surrounding the nucleus (ring sideroblasts). Diagnosis can be ascertained by sequencing the ABC7 gene.

TREATMENT

Standard Therapies: The disorder is not responsive to treatment with pyridoxal phosphate, unlike other forms of XLSA. The favorable long-term prognosis of the spinocerebellar syndrome calls for early physical, occupational, and speech therapy and appropriate educational placement.

Investigational Therapies: Iron supplementation may have adverse effects, underlining the importance of differentiation of XLSA/A from other iron deficient anemias.

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18 Hereditary Angioedema

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DEFINITION: Hereditary angioedema is characterized by recurrent, circumscribed, nonpitting, subepithelial edema involving primarily the extremities, larynx, face, and gut.

SYNONYMS: Hereditary angioneurotic edema; Congenital C1 esterase inhibitor deficiency.

DIFFERENTIAL DIAGNOSIS: Acquired C1 esterase inhibitor deficiency; Angiotensin-converting enzyme inhibitor-induced angioedema; Allergic angioedema; Histamine-induced angioedema; Idiopathic angioedema.

SYMPTOMS AND SIGNS: Angioedema describes deep swelling of the dermis. Lesions usually involve a subcutaneous site (the face or one limb) and are well-circumscribed, nonerythematous, and resolve without sequelae. Pain, urticaria, and pruritis are unusual. Visceral involvement, a consequence of edema in the submucosa and serosa of the bowel wall, results in symptoms ranging from nausea and vomiting to severe colic, sometimes followed by watery diarrhea. Pharyngeal involvement is characterized by progressive symptoms of throat discomfort, dysphagia, dysphonia, and stridor that are accompanied by swelling of the epiglottis, vocal folds, and/or surrounding laryngeal structures. Lesions may extend into the larger bronchi. Death by asphyxiation can occur. Most symptoms last 1–4 days without therapy, and most patients have one or more attacks per month, although episodes can be separated by periods of remission ranging from days to years.

ETIOLOGY/EPIDEMIOLOGY: The incidence is approximately 1 in 50,000 to 1 in 150,000 and the disease can affect any age group. The gene for C1 esterase inhibitor has been

mapped to chromosome 11. The genetic defect is a consequence of many different mutations and is usually transmitted as an autosomal-dominant trait with high penetrance. Approximately 20% of patients have spontaneous mutations. The result is either a deficiency of C1 inhibitor protein (type I) or normal levels of dysfunctional inhibitor in serum (type II).

DIAGNOSIS: Diagnosis relies on a history of episodic angioedema. Trauma, surgery, and emotional stress may precipitate acute episodes. During an episode, serum CH50, C2, and C4 are low, but the C3 level is normal. During remission, CH50 and C2 are usually normal but C4 remains low in 80%–85% of cases. A low (<30%–50% of normal) immunoassayed level of serum C1 inhibitor confirms the diagnosis (type I). In 15% of affected patients, the immunoassayed C1 inhibitor is normal but a bioassay shows low C1 inhibitor activity (type II).

TREATMENT

Standard Therapies: Acute attacks do not usually respond to epinephrine, antihistamines, or corticosteroids. Prevention of asphyxiation from laryngeal swelling requires expert emergency airway management and concurrent intravenous administration of C1 inhibitor concentrate. If not available, fresh frozen plasma may be useful to replace C1 inhibitor levels. Urgent tracheal intubation or cricothyroidotomy/tracheostomy may be needed if the process is rapidly progressive or nonresponding. Abdominal symptoms are generally treated supportively, sometimes with narcotics. Cutaneous symptoms may take longer to respond. Reduction in the frequency and severity of attacks can be achieved with stanozolol. Prophylaxis with androgens is problematic, especially in children. Side effects may limit use, and liver enzymes should be checked at least every 6 months. Antifibrinolytics, such as aminocaproic or tranexamic acid, are less effective. Patients requiring surgery, particularly dental surgery, are at high risk for developing laryngeal angioedema. Treatment with danazol or

stanazolol 5–7 days preoperatively, and C1 inhibitor concentrate or fresh frozen plasma 24 hours before the operation, is recommended. Angiotensin-converting enzyme inhibitors may elevate kinin levels and should be avoided.

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19 Congenital Antithrombin III Deficiency

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DEFINITION: Because antithrombin III (AT III) limits blood coagulation, congenital antithrombin III deficiency is characterized by a marked tendency toward venous or arterial thrombosis. The three recognized forms of the disorder are classic AT III deficiency and two variants, AT III-1a and AT III-1b.

SYMPTOMS AND SIGNS: Patients usually have the first episode of thrombosis between the ages of 10 and 35. Precipitating events include surgery, pregnancy, childbirth, trauma, or use of oral contraceptives. Because pregnancy and estrogen use are significant risk factors, women tend to develop thromboses at an earlier age than men. Approximately 40% of patients with congenital AT III deficiency develop pulmonary embolisms. Embolisms also commonly occur in the veins deep in the legs and pelvic region, the more superficial veins in the legs, and the mesenteric veins. Edema is common in affected legs and pelvic areas. Clots that form in the heart may result in thromboembolism to other organs, such as the brain or kidneys.

ETIOLOGY/EPIDEMIOLOGY: Congenital AT III deficiency is inherited as an autosomal-dominant gene. In the classic form of the disorder, an insufficient amount of antithrombin is produced in the liver. In the variant forms, AT III-1a and AT III-1b, both normal and abnormal AT III are produced but interact so that inhibition of normal antithrombin results. The disease is estimated to occur in approximately 1 in 3,000 to 1 in 5,000 individuals.

DIAGNOSIS: Diagnosis of AT III is confirmed by the blood AT III assay. Any individual with a history of venous

thromboembolism before the age of 40 should be evaluated for AT III deficiency even if the blood level is normal. Patients who have any of the following characteristics should be screened for AT III deficiency: a family history of thrombosis, a thrombosis before age 35, recurrence of thrombosis even with heparin therapy, deep vein thrombosis early in pregnancy, or loss of large amounts of protein in the urine. Studies suggest that early diagnosis and treatment may reduce the incidence of thrombosis.

TREATMENT

Standard Therapies: The goal of treatment is to prevent thrombosis, primarily through the use of oral anticoagulants, such as coumadin drugs, heparin, and intravenous concentrated AT III. The orphan drug Thrombate III (Bayer Corporation) is now a standard therapy. When the risk of thrombosis is high, as during pregnancy or with surgery, AT III replacement therapy is particularly important. AT III should also be replaced to help dissolve blood clots after thrombosis has occurred. Heparin and AT III replacement can cause bleeding, so the therapy must be carefully monitored. AT III can also increase the patient's risk of developing hepatitis, because it is derived from pooled plasma. Women who are prone to this disorder should refrain from taking estrogen. A drug known as AT nativ (Kabivitrum) has been approved as a treatment for congenital AT III deficiency. The use of anticoagulants may prevent recurrences.

Investigational Therapies: AT III replacement is under development. Human AT III is being investigated to determine its safety and efficacy in preventing or arresting episodes of thrombosis in patients with congenital AT III deficiency, especially those who have suffered trauma or are about to undergo surgery or childbirth.

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20 Banti Syndrome

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DEFINITION: The name Banti syndrome is an old descriptor for cases of portal hypertension and splenomegaly in the absence of significant hepatic disease or portal or hepatic venous thrombosis.

SYNONYMS: Idiopathic portal hypertension; Noncirrhotic portal fibrosis.

DIFFERENTIAL DIAGNOSIS: Cirrhosis; Portal vein thrombosis; Hemolytic anemia; Hematologic malignancy; Nodular regenerative hyperplasia; Partial nodular transformation of liver; Early primary biliary cirrhosis; Hepatic sarcoidosis; Venoocclusive disease of liver.

SYMPTOMS AND SIGNS: Individuals with Banti syndrome usually present in adulthood with portal hypertension and splenomegaly. The disease is usually asymptomatic; bleeding from esophageal or gastric varices may be the first sign. Liver function is well preserved, and jaundice, ascites, and encephalopathy are rare. The liver may be normal sized or slightly enlarged. If arsenical intake is implicated, palmar skin keratosis and melanosis may be present.

ETIOLOGY/EPIDEMIOLOGY: Banti syndrome is relatively common in parts of India and Japan, but rare in Western countries. Arsenic intake has been implicated; the condition has been reported in patients taking long-term arsenical preparations such as Fowler solution for psoriasis. Increased arsenic levels are present in drinking water in some countries and may contribute to regional differences in incidence. Cases have occurred in patients taking

long-term azathioprine, particularly after kidney transplantation, and workers exposed to vinyl chloride have developed idiopathic portal hypertension as well as angiosarcoma. The precise mechanisms for splenomegaly and portal hypertension are not fully understood. Increased resistance to portal venous flow through the liver is probably the most important factor, although increased splenic blood flow may also play a role.

DIAGNOSIS: The diagnosis should be suspected if splenomegaly and portal hypertension exist in the presence of a near normal liver biopsy and patent portal and splenic veins.

TREATMENT

Standard Therapies: If an etiologic factor such as arsenic or azathioprine is identified, the exposure should be stopped. The main clinical problem is bleeding esophageal or gastric varices. Because liver function is usually well preserved, the prognosis for bleeding is more favorable than when hepatic cirrhosis is present. Treatment is the same as for other causes of portal hypertension. If large varices are identified before bleeding occurs, prophylactic β -blockade or endoscopic banding should be considered. Active bleeding may be treated with vasoconstrictor drugs and/or endoscopic sclerotherapy or banding as appropriate. With resistant or recurrent bleeding, transjugular shunt or surgical shunt may be necessary.

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21 Bernard-Soulier Syndrome

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DEFINITION: Described first in 1948, the Bernard-Soulier syndrome is an inherited platelet bleeding disorder characterized by thrombocytopenia, giant platelets, and an abnormality in platelet–vessel wall interaction owing to a deficiency in the platelet membrane glycoprotein (GP) Ib-V-IX complex.

DIFFERENTIAL DIAGNOSIS: Congenital thrombocytopenia; Autoimmune thrombocytopenia; May-Hegglin anomaly; Gray platelet syndrome.

SIGNS AND SYMPTOMS: Patients have mucocutaneous bleeding, including purpura, epistaxis, gingival bleeding, and menorrhagia. Bleeding into joints or deep visceral hematomas are uncommon. Severity of symptoms is highly variable from easy bruising to recurrent and severe spontaneous bleeding starting from birth. Intensity of manifestations may vary among affected family members. The physical examination is otherwise unremarkable. These patients do not have splenomegaly.

ETIOLOGY/EPIDEMIOLOGY: Bernard-Soulier syndrome is inherited as an autosomal-recessive trait. No prevalence data are available. Platelets are deficient in platelet membrane GPIb, GPIX, and GPV, which exist as a complex. GPIb is a platelet receptor for von Willebrand factor (vWF). Following injury to the blood vessel, platelets adhere to the subendothelium by binding of vWF to platelet GPIb. This process (adhesion) is impaired in Bernard-Soulier syndrome. The syndrome arises owing to mutations in the genes governing GPIb (which consists of two peptides, GPIb α and GPIb β) and GPIX.

DIAGNOSIS: Most patients have moderate thrombocytopenia (50,000–100,000/ μ L) with large platelets on the pe-

ripheral smear. Bleeding time is prolonged, with normal prothrombin time and activated partial thromboplastin time. In platelet aggregation studies, the responses to ADP, epinephrine, and collagen are normal. Characteristically, platelet agglutination by ristocetin is absent or decreased, and this is not corrected by normal plasma. Plasma levels of factor VIII and vWF factor are normal. The diagnosis is confirmed by demonstrating that platelet GPIb is decreased on platelets. Heterozygotes have normal platelet counts and platelet function, but their platelets may be abnormally large. They have intermediate concentrations of GPIb-IX-V complex on platelets.

TREATMENT

Standard Therapies: Platelet transfusions are indicated for control of clinically significant bleeding manifestations and in relation to surgical procedures. Some patients may develop antibodies to GPIb following platelet transfusions, and these antibodies may compromise the efficacy of subsequent platelet transfusions. Splenectomy or corticosteroids are not indicated in these patients. Administration of desmopressin may be beneficial in controlling bleeding manifestations in some patients.

Investigational Therapies: Recombinant factor VIIa is under investigation.

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22 Chédiak-Higashi Syndrome

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DEFINITION: Chédiak-Higashi syndrome (CHS) is an autosomal-recessive disorder characterized by increased susceptibility to infection due to defective degranulation of neutrophils, mild bleeding diathesis, partial oculocutaneous albinism, progressive peripheral neuropathy, and a tendency to develop a life-threatening lymphoma-like syndrome.

SYNONYMS: Béguez-César disease; Chédiak-Higashi anomaly; Chédiak-Steinbrinck-Higashi syndrome.

DIFFERENTIAL DIAGNOSIS: Other genetic forms of partial albinism; Acute and chronic myelogenous leukemias.

SYMPTOMS AND SIGNS: Patients with CHS have light skin and silvery hair. They frequently complain of solar sensitivity and photophobia. Other symptoms and signs vary considerably, but frequent infections and neuropathy are common. The infections involve the mucous membranes, skin, and respiratory tract. Affected children are susceptible to gram-positive and gram-negative bacteria and fungi, most commonly *Staphylococcus aureus*. The neuropathy may be central and motor in type, and ataxia may be a prominent feature. Neuropathy often begins in the teenage years and becomes the most prominent problem. Patients with CHS may have prolonged bleeding times with normal platelet counts, resulting in impaired platelet aggregation associated with a platelet storage pool disorder. Natural killer cell function is also impaired, leading to inability on the part of the patient to contain Epstein-Barr virus. When patients are infected with Epstein-Barr virus, they are susceptible to entering the accelerated phase of the disorder characterized by marked enlargement of the liver, spleen, and lymph nodes.

ETIOLOGY/EPIDEMIOLOGY: The syndrome is inherited in an autosomal-recessive pattern. It is caused by a mutation in the gene for CHS located on chromosome 1q42-q44. The gene encodes a cytosolic protein named

lysosomal-trafficking regulator, which has structural features homologous to a vacuolar sorting protein, termed VPS15 yeast. This CHS protein is believed to be associated with vacuolar transport in the Golgi apparatus or molecular sorting in endosomes.

DIAGNOSIS: The diagnosis is established by finding large inclusions in all nucleated blood cells. These can be seen on Wright-stained blood films, but are accentuated in the cells of the myeloid series by a peroxidase stain.

TREATMENT

Standard Therapies: Treatment is generally supportive. High doses of ascorbic acid improve the clinical status of some patients in the stable phase. It has been shown *in vitro* to correct the chemotactic defect. Although the efficacy of the vitamin is controversial, given its safety, it is reasonable to administer ascorbic acid to all patients. The only curative therapy for the accelerated phase is bone marrow transplantation from an HLA-compatible donor or unrelated donor compatible at the D locus. Stem cell transplantation reconstitutes normal hematopoietic and immunologic functions and corrects the natural killer cell deficiency; however, it does not correct or prevent the peripheral neuropathy, although it may benefit the central neuropathy.

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23 Chylomicron Retention Disease

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DEFINITION: Chylomicron retention disease is an autosomal-recessive disorder characterized by the selective absence of the apolipoprotein (apo) B48-containing lipoproteins, chylomicrons, in the plasma. This results in fat malabsorption with the consequences of steatorrhea, hypolipidemia, vitamin A and E deficiency, slight acanthocytosis, mental and growth retardation, and nervous system disorders.

SYNONYM: Anderson disease.

DIFFERENTIAL DIAGNOSIS: Abetalipoproteinemia; Hypobetalipoproteinemia.

SYMPTOMS AND SIGNS: Patients usually present in early infancy with steatorrhea and growth and mental retardation. Neurologic signs, such as the loss of deep tendon reflexes, are variable and not as severe as in abetalipoproteinemia and hypobetalipoproteinemia. Furthermore, acanthocytosis and retinitis pigmentosa are seldom seen in chylomicron retention disease.

ETIOLOGY/EPIDEMIOLOGY: The molecular and genetic mechanisms responsible for the disease are unknown; however, the disease may be related to defects in chylomicron secretion.

DIAGNOSIS: Diagnosis is based on the determination of plasma lipid and apoB levels and microscopic analysis of intestinal biopsies. Low plasma levels of apoB100 and ab-

sence of apoB48 are diagnostic features. In addition, low plasma cholesterol levels (<75 mg/dL), half the normal low-density lipoprotein levels, and normal plasma triglycerides (TG) are observed. The lack of postprandial rise in plasma TG levels is characteristic. Intestinal biopsy shows normally structured villi that contain abnormal enterocytes loaded with lipid droplets. Endoscopy shows a snowy white epithelium.

TREATMENT

Standard Therapies: A low-fat diet supplemented with lipid-soluble vitamins A and E and essential fatty acids should be implemented as early as possible, to allow the patient a return of normal growth and abatement of gastrointestinal symptoms. Patient compliance with the dietary regimen is vital; departure from the low-fat diet results in rapid relapse and recurrence of symptoms.

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24 Ewing Sarcoma of Bone

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DEFINITION: Ewing sarcoma (ES) of bone is a malignant tumor in the Ewing family of tumors (ES of bone, extrasosseous ES, and primitive neuroectodermal tumors).

The tumor most commonly arises from the bones of the pelvis/sacrum, proximal extremity, or distal extremity. Rarely, ES may arise from other bones or soft tissue.

SYNONYM: Ewing tumor.

DIFFERENTIAL DIAGNOSIS: Osteosarcoma; Chondrosarcoma; Osteochondromas; Lymphoma; Medulloblastoma; Small cell carcinoma; Neuroblastoma.

SYMPTOMS AND SIGNS: Individuals with ES often experience tumor-associated pain and swelling, fever, anemia, and abnormally increased levels of circulating white blood cells (leukocytosis). Ewing sarcoma can be associated with preexisting skeletal abnormalities (such as enchondromas and aneurysmal bone cysts) and genitourinary abnormalities (such as hypospadias and duplicate collecting systems).

ETIOLOGY/EPIDEMIOLOGY: Ewing sarcoma affects males more often than females and usually develops when a person is between the ages of 10 and 20 years. The exact cause is unknown. Earlier trauma to the area of involvement is sometimes a preceding factor.

DIAGNOSIS: Diagnosis is made by histopathology. The *MIC2* gene product (CD99) is a surface protein found on most ES and its presence may aid in diagnosis. Ewing sarcoma tends to metastasize to the lungs and/or bones; therefore, radiographic evaluation generally includes chest radiography, CT of the chest, and a bone scan. Plain films, CT, and/or MRI of the primary tumor may be helpful in defining the extent of soft tissue involvement, determining bone marrow invasion, and in planning surgical therapy. Some clinicians perform a bone marrow biopsy to evaluate whether the tumor has metastasized to the bone marrow. The most common sites of marrow metastases are the vertebral bodies; a screening MRI of the entire spine is the most sensitive test to detect bone marrow involvement.

TREATMENT

Standard Therapies: The optimal treatment approach is systemic chemotherapy with surgery or radiotherapy as an adjunct for local control. Surgery alone offers long-term survival rates of less than 10% due to occult but aggressive metastatic disease. It is used as an adjuvant for local control, often with an attempt at limb preservation. Radio-

therapy offers excellent local control, but no prospective studies have been done to compare it with surgery. Radiation therapy alone gives local control of 44%–86% with a long-term survival rate of 16%–25%. Multimodality therapy provides an overall survival rate of approximately 56% at longer than 3 years. Most studies give 12–18 months of chemotherapy with 3–6 cycles before local therapy. Total duration of chemotherapy can now be shorter (often less than 12 months) because of dose-intensive therapy with the use of marrow-stimulating growth factors.

Investigational Therapies: The drug gemcitabine has shown activity in soft tissue sarcomas and is currently available at M.D. Anderson Cancer Center for patients with advanced ES and other bone tumors. The drug liposomal N-acetylglucosiminy-N-acetylmuramyl-L-Ala-D-isoGln-L-Ala-glycerolipalmitoyl (ImmTher) has received an orphan drug designation for its use in the treatment of ES, but more studies are needed to determine its long-term safety and effectiveness. Various combinations of chemotherapeutic agents, total body irradiation, and stem cell transplantation are being evaluated as effective therapy for high-risk ES.

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25 Factor IX Deficiency

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DEFINITION: Factor IX deficiency is an inherited bleeding disorder caused by a diminished or absent amount of factor IX, an important protein in the hemostatic system.

SYNONYMS: Hemophilia B; Christmas disease.

DIFFERENTIAL DIAGNOSIS: Factor VIII deficiency (hemophilia A).

SYMPTOMS AND SIGNS: The lack of factor IX leads to impaired thrombus formation and thus prolonged and

often severe bleeding from various sites. Patients with factor IX deficiency are categorized as having severe disease if they have less than 1% factor IX activity, moderate with 1%–5% activity, and mild with 5%–15% activity. Severe factor IX deficiency leads to spontaneous hemorrhage, with the most common sites being joints and mucous membranes. Bleeding, however, can occur from anywhere, including the central nervous system, deep muscles, retroperitoneum, and visceral organs. Patients with moderate hemophilia occasionally have spontaneous hemorrhage; more often, however, they have significant bleeding after minor trauma. Patients with a mild deficiency bleed only after trauma, but the severity is out of proportion to the level of trauma. All patients with hemophilia have excessive bleeding after invasive procedures, no matter how minor, and require prophylactic therapy even for immunizations. Inadequately treated joint bleeding leads to chronic arthropathy, which results in severe joint dysfunction.

ETIOLOGY/EPIDEMIOLOGY: Factor IX deficiency is an X-linked recessive disorder caused by various mutations in the gene for factor IX. It occurs in 1 of 30,000 males, with the severe form accounting for most patients. All ethnic groups are affected equally. Female carriers of factor IX deficiency may be symptomatic due to nonrandom X chromosome inactivation. They have a phenotype similar to mild hemophilia.

DIAGNOSIS: Factor IX deficiency should be suspected in any male with prolonged or unusual bleeding symptoms. Common presentations in infancy include prolonged bleeding after circumcision or heel sticks, swelling after immunizations, and a known history of hemophilia in maternal relatives. Beyond infancy, patients may present with joint hemorrhages, mucous membrane bleeding, or excessive bleeding after trauma. A coagulation evaluation should be undertaken, including a platelet count, prothrombin time, and activated partial thromboplastin time

(aPTT). Patients with factor IX deficiency will have a prolonged aPTT. With this finding, specific factor assays should be done for factors VIII and IX. The patient has hemophilia B if the factor IX activity is less than 15%.

TREATMENT

Standard Therapies: The treatment is replacement of factor IX by concentrates in the form of either recombinant protein or plasma-derived protein. The major benefit of recombinant factor IX is the low risk of viral transmission. Patients with severe factor IX deficiency may receive either prophylactic or on-demand therapy. Those who have intracranial hemorrhage or recurrent joint hemorrhage should receive prophylactic therapy. Patients with mild to moderate hemophilia generally receive only on-demand therapy because they bleed less frequently and are less likely to develop chronic joint disease. All invasive procedures require replacement of factor IX before the procedure.

Investigative Therapies: Gene therapy is being researched.

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26 Factor XII Deficiency

Robert W. Colman, MD

DEFINITION: Factor XII (FXII) deficiency is an abnormality in a plasma protein inherited as an autosomal-recessive trait. The trait is characterized by a prolonged activated partial thromboplastin time (aPTT) in the absence of an associated clinical bleeding disorder.

SYNONYM: Hageman trait.

DIFFERENTIAL DIAGNOSIS: Prekallikrein deficiency; High molecular weight kininogen deficiency.

SYMPTOMS AND SIGNS: In patients with congenital FXII deficiency, there is probably an increased incidence of

venous thromboses and acquired thrombotic disorders, such as myocardial infarction and rethrombosis of coronary arteries after thrombolytic therapy.

ETIOLOGY/EPIDEMIOLOGY: FXII is coded for by a single gene of 12 kb that maps to chromosome 5, comprising 13 introns and 14 exons. Most Hageman trait plasma lacks both functional and antigenic (CRM-) FXII. Immunoreactive FXII cross-reacting material (CRM+) has been recognized in three patients who lack functional FXII activity. Individual patients of Swiss, Asian, and Italian extraction are noted to have decreased levels of FXII. The molecular basis of several types of CRM-FXII has been elucidated. In one family, a T-to-C transition leads to a transversion of the transcription initiator site. In a second family, a splice site mutation in the FXII gene results in a truncated transcript and a lack of circulatory FXII protein. Defects in the light chain of FXII result in disorders of the enzymatic activity of the protein.

DIAGNOSIS: In patients with prolonged aPTT who have no history of a bleeding disorder, the most likely diagnosis is the acquired condition of a lupus anticoagulant, part of the antiphospholipid syndrome. Therefore, this syndrome should be ruled out by specific tests incriminating an antibody to phospholipid-plasma protein complexes. If the results of these tests are negative, assays

for FXII, pyruvate kinase, and HK as well as factor XI should be performed.

TREATMENT

Standard Therapies: No treatment is required in the asymptomatic individual. If FXII deficiency is associated with deep venous thrombosis, anticoagulation with warfarin or low molecular weight heparin is indicated. The anticoagulant should be extended for at least 6 months and possibly indefinitely.

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27 Glanzmann Thrombasthenia

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DEFINITION: Glanzmann thrombasthenia is an inherited bleeding disorder caused by defects in the platelet membrane receptor α IIb β 3, which results in a lifelong mucocutaneous bleeding diathesis of variable severity.

DIFFERENTIAL DIAGNOSIS: von Willebrand disease; Mild factor VIII or factor IX deficiency; Immune thrombocytopenia; Afibrinogenemia; Dysfibrinogenemia; Hermanski-Pudlak syndrome; Bernard-Soulier syndrome; Chédiak-Higashi syndrome; Wiskott-Aldrich syndrome; Gray platelet syndrome; Hypersplenism; Cardiac disease; Liver disease; Renal disease.

SYMPTOMS AND SIGNS: Most patients are diagnosed before age 5, many at birth or in infancy. Epistaxis, purpura, and gingival bleeding are the most common symptoms, and may be more pronounced in children. Spontaneous petechiae are rare except in the newborn period, where they may represent an exaggeration of the normal newborn petechiae observed after birth trauma. Epistaxis is the most common form of bleeding and may be life threatening. In adolescent and adult women, menorrhagia is common and may be severe, particularly at menarche. Gastrointestinal bleeding and hematuria may occur, but are less common. Other types of bleeding are uncommon, and spontaneous hemorrhage is rare. Hemarthroses and intracranial hemorrhages have been reported, but are usually associated with trauma. Bleeding after trauma or minor surgery can be severe, and patients are frequently di-

agnosed after circumcision or tooth extraction. Parturition and postpartum bleeding may be severe, and the risk extends for at least 2 weeks postpartum. Most patients will at some point experience bleeding severe enough to require red cell and/or platelet transfusions.

ETIOLOGY/EPIDEMIOLOGY: This autosomal-recessive disease results from mutations in the genes encoding either the α IIb or β 3 integrin subunits. Approximately 60 patients have been reported. Many additional cases have likely gone unreported or undiagnosed. The disease is more common in populations with a high degree of intra-group marriage, such as in the Middle East, India, and France.

DIAGNOSIS: Patients have normal platelet counts and morphology; normal prothrombin time, partial thromboplastin time, and coagulation factor levels; and markedly prolonged bleeding times. Platelet aggregation is normal in response to ristocetin but absent or severely diminished in response to adenosine diphosphate, collagen, epinephrine, and other agonists. Clot retraction may be absent, decreased, or normal, depending on the nature of the defect. Heterozygous carriers usually have no clinical symptoms.

TREATMENT

Standard Therapies: Acute severe hemorrhage is usually controlled by platelet transfusion, but may require red cell transfusion. Iron deficiency is common due to chronic blood loss, particularly from gingival bleeding. Patients should maintain good dental hygiene and receive iron sup-

plementation as needed. Platelets should be given before any invasive procedure and continued until the wound has healed. Mechanical packing and cauterization of mucosal vessels may be required for severe epistaxis. Tranexamic acid and epsilon aminocaproic acid may help to control minor bleeding, and can be given as an adjunct to platelets for tooth extraction. Using hormonal therapy to induce amenorrhea may eliminate menorrhagia.

Investigational Therapies: Recombinant factor VIIa has been reported to be effective in treating bleeding, but it has a potential thrombotic risk. A few patients received allogeneic bone marrow transplants for severe, recurrent bleeding and were cured of disease.

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28 Glioblastoma Multiforme

Mustafa Saad, MD,
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DEFINITION: Glioblastoma multiforme is the most malignant and rapidly growing category of astrocytomas.

SYNONYM: Grade 4 astrocytoma.

DIFFERENTIAL DIAGNOSIS: Other intracranial neoplasm including metastatic lesion; Brain abscess; Tuberculoma; Toxoplasmosis; Stroke.

SYMPTOMS AND SIGNS: The clinical presentation of glioblastoma multiforme is similar to that of other brain tumors except that the onset and progression are more

acute because of its rapid growth. The duration of symptoms is relatively short, ranging from weeks to a few months. Depending on the site, glioblastoma produces symptoms by a combination of compression, infiltration, vascular compression, and increase in intracranial pressure. These include headaches, vomiting, drowsiness, lethargy, seizures, focal neurologic deficits, and mental state changes. The headaches classically occur more at awakening, change with posture, and are accompanied by nausea and vomiting. Mostly, however, they are nonspecific and difficult to differentiate from chronic tension headaches. Bilateral papilledema is present in 25% of cases. Other signs of increased intracranial pressure, such as changes in temperature, blood pressure, pulse, or respiratory rate, are usually present only in the terminal stages of the disease.

ETIOLOGY/EPIDEMIOLOGY: Glioblastoma multiforme is the most common form of glial tumor and is responsible for most of the 12,000 brain tumor–associated deaths that occur in the United States annually. Glioblastoma multiforme tends to occur mainly in an older age group, with peak incidence in the sixth decade. They are more common in whites as compared to other races and have a male:female ratio of 1.5:1. There is an increased incidence of these tumors in patients with neurofibromatosis, tuberous sclerosis, Turcot syndrome, and Li-Fraumani syndrome, in addition to an increased incidence in certain families. The role of environmental factors in their pathogenesis is unknown, with the strongest association found with ionizing radiation given in childhood.

DIAGNOSIS: A brain tumor should be considered in any patient older than 40 years with recent onset of persistent headaches, vomiting, seizures, or focal cerebral deficits. Fundoscopy should be performed to look for papilledema. Diagnosis is done by means of CT or MRI. Chest radiography should also be ordered to look for a likely source of metastasis, if a secondary metastatic lesion is suspected. Histologic diagnosis is usually carried out after surgical resection of the tumor.

TREATMENT

Standard Therapies: There is no curative treatment. The various treatment modalities are used to help provide a better quality and prolongation of life. Standard treatment

for newly diagnosed patients involves maximum feasible resection of the tumor, followed by limited field radiation therapy, with adjuvant chemotherapy using any of the nitrosourea agents. The median survival time is 10 months, compared with 4 months in those who are not treated. Supporting therapy includes glucocorticoids for cerebral edema, anticonvulsants for seizures, and anticoagulants for venous thromboembolic disease. Patients with neurologic deficits may require physical, occupational, and speech therapy.

Investigational Therapies: These include immunotherapy involving interferons, interleukins, activated killer cells to destroy the tumor cells, gene therapy to produce defective viruses that home in and destroy tumor cells, and other ways of inhibiting the growth factor and angiogenesis involved in the growth of brain tumors.

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29 Glucose-6-Phosphate Dehydrogenase Deficiency

**Theresa W. Gauthier, MD,
and Martha H. Manar, MD**

DEFINITION: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a disorder of the red blood cells. Many different mutations of the enzyme occur and are known by such names as G6PD A-, G6PD Mediterranean, and G6PD Union deficiencies.

DIFFERENTIAL DIAGNOSIS: Unstable hemoglobin syndromes; Hereditary nonspherocytic hemolytic anemia due to pyruvate kinase deficiency; Glucose-phosphate isomerase deficiency; Hexokinase deficiency.

SYMPTOMS AND SIGNS: Mild forms of G6PD deficiency, such as G6PD A- deficiency, are characterized by

hemolytic anemia on exposure to oxidizing drugs including primaquine, furadantin, and diaminodiphenylsulfone. In these forms, young erythrocytes generally have normal or near-normal G6PD activity and the hemolytic anemia is self-limited. With severe forms, such as G6PD Mediterranean deficiency, even young red cells are severely deficient. Many infectious diseases can also trigger hemolytic anemia in the G6PD-deficient patient. In some forms, ingestion of fava beans will produce hemolytic anemia. The most serious clinical consequence of G6PD deficiency, which affects only a small subset of G6PD-deficient newborns, is neonatal jaundice, which can lead to kernicterus. These are usually infants who have also inherited the UDPGT1 promoter mutation that causes Gilbert disease. The common (polymorphic) forms of G6PD deficiency are associated with hemolytic anemia only in the presence of stress such as drug administration or infection,

but some less common variants are functionally so severe that they are associated with chronic hemolysis. These are designated as class I variants, and the clinical syndrome is hereditary nonspherocytic hemolytic anemia.

ETIOLOGY/EPIDEMIOLOGY: The gene encoding G6PD is located on the X chromosome, and the disorder is transmitted in a sex-linked fashion. Males are fully affected; females possess a mosaic of red cells, some normal and some deficient. The ratio of deficient to normal cells varies markedly in heterozygotes. More than 100 mutations of G6PD have been characterized at the DNA level, and many more have been described as being distinct on the basis of their biochemical characteristics. The prevalence of G6PD mutations and the type of mutation found varies among populations. In the Mediterranean region, G6PD Mediterranean deficiency is the most common variant and has a gene frequency that varies from less than 1% to more than 50%. Among African Americans, the gene frequency of G6PD A- deficiency is approximately 0.11.

DIAGNOSIS: Diagnosis is easily established on blood samples from males using enzyme assay or a screening test. In mild variants, however, the residual cells after a hemolytic episode may have normal or near normal enzyme activity. Sequencing of the G6PD gene is the most accurate way of establishing a diagnosis in heterozygous females.

TREATMENT

Standard Therapies: If the hemolytic anemia is drug induced, the drug should be discontinued. Generally, no therapy is needed, but blood transfusion may be required in the treatment of severe hemolytic episodes. Vitamin E has been used in chronic nonspherocytic hemolytic anemia due to G6PD deficiency, but not with uniform or convincing success. Splenectomy sometimes helps. Infants with neonatal icterus should be treated with phototherapy and/or exchange transfusion.

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30 Chronic Granulomatous Disease

Mary Dinauer, MD, PhD

DEFINITION: Chronic granulomatous disease (CGD) is an inherited immunodeficiency characterized by serious, recurrent bacterial and fungal infections and episodes of granulomatous inflammation. Symptoms usually begin in infancy or childhood. The disorder results from defects in the production of oxidants by neutrophils and other phagocytic leukocytes, leading to abnormalities in host defense and inflammation.

SYNONYMS: Chronic dysphagocytosis; Granulomatosis, chronic, familial; Granulomatosis, septic, progressive; Fatal granulomatous disease of childhood; Congenital dysphagocytosis.

DIFFERENTIAL DIAGNOSIS: Leukocyte adhesion deficiency; Wegener's granulomatosis; Sarcoidosis.

SYMPTOMS AND SIGNS: CGD is characterized by repeated bacterial and fungal infections that can involve the skin, lymph nodes, lungs, liver, or bones. Perirectal infections or brain abscesses can also occur. Infections are commonly due to *Staphylococcus aureus* as well as gram-negative bacteria (including *Serratia marcescens* and *Burkholderia cepacia*), *Nocardia*, and fungal species such as *Aspergillus* that normally do not cause infections. Some patients also develop granulomatous inflammation, possibly involving the skin; gastrointestinal tract, which can result in gastric outlet obstruction or colitis-like symptoms; or genitourinary tract, which can lead to obstruction. Granulomas are also seen in sites of chronic bacterial or fungal infection. Poor growth and an enlarged liver or spleen can occur. Blood analysis often shows signs of chronic inflammation, with leukocytosis and hypergammaglobulinemia. Symptoms usually begin in infancy or childhood, but some individuals with milder forms of the disease are well until their teens or even adulthood.

ETIOLOGY/EPIDEMIOLOGY: Prevalence is estimated at 1 in 250,000 individuals from all ethnic groups. Four subgroups exist, resulting from genetic defects in any one of four subunits of leukocyte enzyme known as the NADPH oxidase that generates superoxide during the respiratory burst. About two thirds of patients have an X-linked recessive form of CGD; therefore, many of the affected patients are male. The remaining patients have autosomal-recessive forms of CGD. In most cases of X-linked CGD, there is a male family history.

DIAGNOSIS: The diagnosis is established by laboratory testing for neutrophil respiratory burst oxidant production. This test is available at many regional medical centers caring for children with immunodeficiencies or at certain reference laboratories. Commonly used methods include the nitroblue tetrazolium (NBT) slide test (which should be done on a freshly drawn blood sample), a flow cytometric assay using dihydrorhodamine (DHR), or chemiluminescence.

TREATMENT

Standard Therapies: Treatment consists of prophylactic antibiotic therapy, such as trimethoprim and sulfamethoxazole. Corticosteroid drugs may be of benefit for granulomatous complications. Prophylactic Actimmune (interferon- γ) (Genentech) is also recommended and is given by intramuscular injection thrice weekly. Acute infections are treated aggressively; other treatment is symptomatic and supportive. With current management, most patients sur-

vive through at least early adulthood. Genetic counseling is recommended for patients and their families.

Investigational Therapies: The National Institutes of Health/National Institute of Allergy and Infectious Diseases (NIH/NAID) is conducting a clinical trial using a nonmyeloablative allogeneic bone marrow transplant protocol, open to children with a history of at least two serious infections and an HLA-identical sibling. Preliminary clinical studies on the use of gene therapy for treatment of CGD have been undertaken by the NIH/NAID and Indiana University School of Medicine.

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31 Hereditary Hemochromatosis

Richard L. Nelson, MD

DEFINITION: Hereditary hemochromatosis (HH) is an inherited, autosomal-recessive disease characterized in homozygotes by increased absorption of dietary iron, with consequent iron deposition in many organs, including the skin, joints, liver, pancreas, and heart. This iron buildup is toxic to many tissues and eventually results in arthritis, cirrhosis, diabetes, or heart failure.

SYNONYMS: Bronze diabetes; Iron overload.

SYMPTOMS AND SIGNS: No symptoms are specific to hemochromatosis, but rather of the aforementioned diseases arising from iron overload.

ETIOLOGY/EPIDEMIOLOGY: HH is believed to be the most prevalent recessive genetic disorder in the Western world. The gene responsible for the most prevalent form of HH, the *HFE* gene, produces a protein that binds β 2-microglobulin. The *C282Y* mutation of the *HFE* gene is the one most commonly associated with clinical HH. The prevalence of HH *C282Y* homozygotes, reported to be 0.005%, is higher in Celtic populations and lower in African-American and Hispanic populations.

DIAGNOSIS: The demonstration of elevated serum ferritin levels and high transferrin saturation, particularly in the presence of end-organ toxicity consistent with the disorder, suggests the diagnosis, which is confirmed by genetic analysis.

TREATMENT

Standard Therapies: The therapy is a course of iron depletion, with frequent blood donation, until the serum ferritin level declines to a range of 10–20 ng/mL, and is kept below 50 ng/mL in follow-up. This goal is maintained by occasional phlebotomy, especially in men and postmenopausal women. The ideal time to initiate therapy is before the appearance of established HH-related diseases, especially cirrhosis and diabetes.

Investigational Therapies: Research is being done on the efficacy of dietary therapy of HH: iron chelation with tannins (tea) and phytates (fiber).

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32 Paroxysmal Cold Hemoglobinuria

**Natalie D. Depcik-Smith, MD,
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DEFINITION: Paroxysmal cold hemoglobinuria (PCH) is a hemolytic anemia characterized by an autoantibody of the IgG subtype with affinity for cold temperatures directed toward the patient's red blood cells.

SYNONYM: Donath-Landsteiner hemolytic anemia.

DIFFERENTIAL DIAGNOSIS: Idiopathic (primary) cold agglutinin disease; Secondary cold agglutinin disease; Chronic cold agglutinin disease; Warm-antibody autoimmune hemolytic anemia; Myoglobinuria; Paroxysmal nocturnal hemoglobinuria.

SYMPTOMS AND SIGNS: Children and adults present with hemoglobinuria, jaundice, and pallor. Fever and abdominal pain are also common. Due to the transient nature of the disease in children, most are in the recovery phase of the illness at the time of presentation. Both children and adults are anemic at onset to varying degrees, with hemoglobins ranging from 25 to 125 g/L (mean, 68 g/L). The hemoglobin level often drops precipitously during an acute attack.

ETIOLOGY/EPIDEMIOLOGY: Most cases of PCH involve children and are self-limited, following a viral illness.

The incidence has been reported as 2%–5% of all cases of autoimmune hemolytic anemia but more than 50% of all immune hemolytic syndromes diagnosed in children. In adults, the disease runs a more chronic, relapsing course. Earliest reports of the disease had identified PCH following infection with *Treponema pallidum*, the agent of syphilis. With the dramatic decline in the prevalence of syphilis, PCH in adults has declined and the current understanding of the adult form of the disease is less clear. No known genetic, sex, or racial risk factors exist, although the disease has been reported in families. Incidence is approximately equal in men and women.

DIAGNOSIS: The peripheral blood smear should be reviewed in cases of suspected hemolytic anemia. Red blood cell morphology is usually normal, but polychromasia and red cell fragmentation is infrequently seen. Spherocytosis and red cell rosetting around neutrophils (Insert Fig. 43) with erythrophagocytosis (Insert Fig. 44) may be a clue to underlying PCH. The gold standard for diagnosis is the Donath-Landsteiner test. The direct antiglobulin test for complement is usually positive, but is not as specific as the Donath-Landsteiner test.

TREATMENT

Standard Therapies: Strict avoidance of cold temperatures is the most important prophylactic measure for the prevention of hemolysis. In general, cross-matching of blood can be accomplished. When transfusion is necessary

due to severe anemia, it should not be delayed. Survival of the transfused red cells is likely similar to that of the patient's own cells. Use of a blood warmer during transfusion is particularly important. Splenectomy (in adult, relapsing cases) has met with mixed success. Corticosteroid therapy is not effective in PCH. Most cases terminate spontaneously and only require supportive therapy for a few days to weeks after onset.

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33 Paroxysmal Nocturnal Hemoglobinuria

Charles J. Parker, MD

DEFINITION: Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired disease that arises as a result of a somatic mutation of the *PIG-A* gene. The primary clinical manifestation of this deficiency is intravascular hemolysis resulting in hemoglobinuria.

DIFFERENTIAL DIAGNOSIS: Antibody-mediated hemolytic anemias, especially paroxysmal cold hemoglobinuria.

SYMPTOMS AND SIGNS: Hemoglobinuria is the presenting symptom in approximately 25% of patients, but essentially all patients have laboratory evidence of ongoing hemolysis. The failure to compensate adequately for the hemolysis is due to underlying bone marrow dysfunction that is an important component of the disease. The disorder arises out of the setting of bone marrow failure syndromes, particularly aplastic anemia. Thus, in addition to anemia with evidence of hemolysis, patients with PNH usually have leukopenia, thrombocytopenia, or both. Another important clinical manifestation is thrombophilia. Female patients with PNH are at increased risk for thrombosis during pregnancy and the puerperium. When closely questioned, many patients with PNH complain of painful or difficult swallowing.

ETIOLOGY/EPIDEMIOLOGY: The disorder is not inherited and results from a somatic mutation affecting a primitive hematopoietic stem cell. The prevalence appears to be in the range of 1 case per $0.5\text{--}1.0 \times 10^6$ population. It

has been described in all ages and many racial groups. It occurs in all parts of the world, but the incidence may be increased in regions where aplastic anemia is more common (e.g., the Far East and Indochina). There may be a slight female predominance.

DIAGNOSIS: The disease is diagnosed most frequently in adults in the fourth and fifth decades, but has been reported in all age groups ranging from children younger than 10 years to elderly adults. The disorder should be suspected in patients with unexplained symptoms or signs of chronic intravascular hemolysis, including hemoglobinuria, hemosiderinuria, and a markedly elevated serum lactate dehydrogenase. These findings coexisting with evidence of bone marrow failure (e.g., thrombocytopenia, leukopenia, or both) suggest PNH arising in the setting of aplastic anemia. The diagnosis of PNH is made by flow cytometry.

TREATMENT

Standard Therapies: Patients should take folate supplements. Serum ferritin should be determined, and supplemental iron given to iron-deficient patients. In some patients, the hemolysis of PNH is ameliorated by prednisone. Some responding patients require maintenance doses of steroids. An every-other-day schedule (not to exceed 15 mg) is favored to diminish the complications of long-term steroid use. If daily steroids are required, the dose should not exceed 10 mg. Few therapeutic options exist for steroid nonresponders. Allogeneic bone marrow transplantation can be curative but is usually reserved for patients with bone marrow failure and those with recurrent life-

threatening thromboembolic disease. Thromboses should be managed with standard anticoagulant therapy, and thrombolytic therapy has been advocated for Budd-Chiari syndrome in the acute setting. Affected females who become pregnant should receive prophylactic heparin through the puerperium.

Investigational Therapies: The benefit of prophylactic coumadin in patients with no history of thromboembolic disease is being studied.

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34 The Hemophilias

Margaret W. Hilgartner, MD

DEFINITION: The hemophilias are a group of bleeding disorders classified by coagulation factor deficiencies.

DIFFERENTIAL DIAGNOSIS: Deficiency of the other coagulation proteins; Platelet and thrombocytopenic abnormalities; Thrombophilic disorders.

SYMPTOMS AND SIGNS: The severity of factor VIII and IX disorders is defined by the degree of clotting factor deficiency in the patient's plasma. The normal plasma range is 50%–120% of each of these factors. Severe disease is found in those with less than 1% plasma level, moderate disease in those with 2%–10%, and mild disease in those with 10%–40%. Patients with severe disease have spontaneous bleeding beginning in early childhood, primarily into their joints, and leading to severe chronic arthropathy of most major joints by adulthood. The carrier female may have clotting factor levels in the range of mild disease, may bruise easily, and have menorrhagia. Patients with severe factor XI deficiency are not prone to spontaneous bleeding, even though their plasma level of factor XI may be very low.

ETIOLOGY/EPIDEMIOLOGY: Hemophilia A (factor VIII deficiency) occurs primarily in males, in 1 in 10,000 live male births, and is transmitted by females. Hemophilia B (factor IX deficiency) occurs in 1 in 750,000 births, again primarily in the male and transmitted by the female. A specific defect exists at a different gene on the X chromosome

for each disorder. Hemophilia C (factor XI deficiency) occurs in 5.5%–8.0% of Ashkenazi Jews and in 1 in 20,000 births among other ethnic groups in both males and females. Four mutations may account for this deficiency. Deficiencies of factors VIII and IX are the most common and potentially severe diseases.

DIAGNOSIS: The diagnosis of a bleeding disorder with either factor VIII or IX deficiency may be suspected when a baby has bleeding from the umbilical cord, routine heel stick, excessive bruising in the neonatal period, following circumcision, or later with bleeding into the knees or elbows when crawling. The activated partial thromboplastin time is markedly prolonged for factor VIII and IX deficiency but not for factor XI deficiency. The diagnosis of factor XI deficiency is usually made later in life when the patient may have bleeding with oral surgery or bleeding of the mucous membrane. The genotype is important in determining whether the patient may bleed with a low plasma factor level. Homozygotes may have more severe bleeding with trauma or surgery than the heterozygote patient.

TREATMENT

Standard Therapies: Treatment is based on replacement of the missing clotting factor. Concentrates of all three factors derived from normal human plasma are available for infusion, as are replacements of factors VIII and IX made by recombinant technology. The preferred treatment is to administer, by repeated infusions, specific recombinant clotting factors two to three times weekly to prevent bleeding episodes. Persons with moderate and mild disease require treatment for each bleeding episode sufficient to control bleeding and to allow for the 3–5 days necessary for healing to occur. If the patient has repeated bleeding into

one joint, prophylactic treatment may be indicated. Several alternative therapies are available for patients with moderate and mild factor VIII disease, including desmopressin and amicar, an antifibrinolytic agent. Bleeding in the patient with factor XI deficiency requires the infusion of fresh frozen plasma. Some patients may require repeated infusions for trauma-induced bleeding and surgery.

Investigational Therapies: Experimental therapy using gene replacement for both factor VIII and IX deficiency is being explored.

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35 Hermansky-Pudlak Syndrome

William A. Gahl, MD, PhD

DEFINITION: Hermansky-Pudlak syndrome (HPS) is an autosomal-recessively inherited disorder characterized by oculocutaneous albinism and a bleeding tendency due to absent platelet dense bodies. Some patients also have pulmonary fibrosis or granulomatous colitis.

DIFFERENTIAL DIAGNOSIS: Oculocutaneous albinism; Ocular albinism; Chédiak-Higashi disease; Platelet storage pool deficiency.

SYMPTOMS AND SIGNS: The oculocutaneous albinism of HPS is variable in degree, but manifests with congenital nystagmus and decreased visual acuity varying from 20/50 to 20/400. Hair, skin, and eyes (irides) are hypopigmented compared with other family members. Iris transillumination and a pale retina are other signs related to albinism. Patients also present with bleeding due to impairment of platelet aggregation. Mucous membranes and soft tissue bleeds include bruising at the time of ambulation, frequent hematomas of unknown origin, heavy menstrual periods, and epistaxis. Prolonged bleeding can occur after tooth extraction, childbirth, and minor surgery. The platelet count, coagulation factors, prothrombin time, and partial thromboplastin time are normal; the bleeding time is often prolonged. Patients with a subtype due to mutations in the *HPS1* or *HPS4* gene are at increased risk for developing pulmonary fibrosis. Symptoms include shortness of breath, fatigue, and cough. Approximately 15% of patients have a granulomatous colitis resembling Crohn disease. Symptoms include cramping and bloody diarrhea. Occasionally, cardiac and renal involvement occurs.

ETIOLOGY/EPIDEMIOLOGY: The disorder can be caused by mutations in at least four genes: *HPS1*, *ADTB3A*, *HPS3*, and *HPS4*. All types of HPS are inherited in an autosomal-recessive fashion, and both genders are equally affected. There is a concentration of approximately 450 patients in northwest Puerto Rico with the same mutation in the *HPS1* gene, and a smaller group of patients in central Puerto Rico, each having an identical mutation in *HPS3*. Outside of Puerto Rico, the incidence of all types of HPS is probably in the range of 1 in 1 million live births.

DIAGNOSIS: Absence of platelet dense bodies on wet-mount electron microscopy in a patient with some degree of hypopigmentation makes the diagnosis. The absence of giant intracellular granules should be documented to rule out Chédiak-Higashi disease. Oculocutaneous albinism is diagnosed by demonstrating horizontal nystagmus and decreased visual acuity, as well as abnormal optic nerve fiber decussation on measurement of visual evoked potentials. Bleeding diathesis can be documented by demonstrating a lack of a secondary aggregation response by platelets, as well as absent dense bodies. A high-resolution CT chest scan should be performed in patients with restrictive lung disease. For patients with gastrointestinal symptoms, a colonoscopy can help confirm the diagnosis of granulomatous colitis.

TREATMENT

Standard Therapies: For oculocutaneous albinism, sun avoidance to prevent skin cancers is the most important intervention. In general, corrective lenses are not helpful. For the bleeding diathesis, intravenous DDAVP (1-desamino-8-D-arginine vasopressin) can be used prior to minor sur-

gical procedures, and topical thrombin and gelfoam can also retard bleeding. For major surgery and profuse bleeding, platelet transfusions are indicated. No therapy exists for the pulmonary fibrosis, but the granulomatous colitis appears to respond to agents that treat Crohn disease, e.g., steroids or tumor necrosis factor- α inhibitors.

Investigational Therapies: Pirfenidone, an investigational antifibrotic agent, is being studied to treat the pulmonary fibrosis of HPS. Lung transplantation has not been performed.

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36 Langerhans Cell Histiocytosis

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DEFINITION: Langerhans cell histiocytosis (LCH) is a nonmalignant proliferation of Langerhans cells (LCs). Children and adults may have LCH in skin, bones, lymph nodes, brain, lung, liver, spleen, and bone marrow (see also Hemophagocytic Histiocytosis entry).

SYNONYMS: Histiocytosis-X; Eosinophilic granuloma; Hand-Schuller-Christian syndrome; Letterer-Siwe disease.

DIFFERENTIAL DIAGNOSIS: Candida infection; Neuroblastoma; Leukemia; Tuberculosis; Ewing sarcoma; Bone cyst; Lymphoma; Storage disease; Portal hypertension; Infiltrative disease of the bone marrow; Congenital cysts.

SYMPTOMS AND SIGNS: Infants often present with an extensive seborrhea-like rash on the scalp, an erythematous papular rash, or deep ulcerative lesions in the groin. Some have purplish brown lesions 3–6 mm in diameter. Marked hypertrophy of the gingiva with early eruption of teeth occurs. Infiltration of the liver and spleen results in massive organomegaly. Liver dysfunction causes hypoproteinemia with edema and ascites. Lymph nodes in the cervical, axillary, and inguinal areas are most often affected, but mediastinal nodes may enlarge, causing wheezing and respiratory compromise. Lung involvement results in tachypnea and pneumothoraces. Bone marrow infiltration causes pancytopenia, but thrombocytopenia is often the most obvious problem, with bleeding and anemia that may be exacerbated by hypersplenism. Bone lesions in children or

adults present as painful lesions. For children the skull is most often affected, followed by long bones of the upper and lower extremity, ribs, and spine. Adults have many more lesions in the mandible and maxilla. Pulmonary involvement is more prevalent in adults. Many adult female patients have ulcerative lesions in the genital tract or groin. Both children and adults may initially present with diabetes insipidus. Patients with cerebellar involvement present with ataxia. Cerebral infiltrations of several types may lead to headaches and behavior changes.

ETIOLOGY/EPIDEMIOLOGY: The etiology is unknown. The disorder occurs in approximately 5 children and 2–3 adults per million population. Several cytokines are expressed at higher levels in the LCs and surrounding lymphocytes. An underlying immune defect is the likely cause of disease, but no specific gene mutations or chromosomal abnormalities have been identified. Patients with LCH have a higher incidence of malignancy, either before or after diagnosis.

DIAGNOSIS: Diagnosis is made by radiography of the skull; a complete skeletal bone survey and bone scan; chest radiography; complete blood count and differential; erythrocyte sedimentation rate; liver function tests, including AST, ALT, bilirubin, and alkaline phosphatase; electrolytes; and urinalysis. CT of the skull is indicated if mastoids are involved. With pulmonary disease, high-resolution CT is indicated, and with brain involvement, MRI is indicated. For diabetes insipidus, a water deprivation test or serum and urine osmolality should be performed.

TREATMENT

Standard Therapies: Treatments vary depending on the extent of disease and involve chemotherapy with prednisone, vinblastine sulfate (Velban) with or without 6-mercaptopurine, and methotrexate. Patients with liver, spleen, lung, or bone marrow involvement are considered to be at higher risk for not responding to therapy. Patients with lesions in multiple bones or more than one risk organ have an excellent chance for responding to combination chemotherapy. If a patient does not respond to the standard therapy by the 6th week (or 12th week for a partial response), they should be changed to the salvage therapy (2-CdA/Ara-C) on the LCH-S protocol. A separate protocol exists for following and treating patients with central nervous system involvement.

Investigational Therapies: Anticytokine therapy is being investigated.

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37 Hyper-IgM Syndrome

Roger H. Kobayashi, MD

DEFINITION: Hyper-IgM syndrome is a primary immunodeficiency disease characterized by recurrent, severe bacterial or opportunistic infections, typically within the first 2 years of life.

SYNONYMS: Immunoglobulin deficiency with increased IgM; X-linked hyper-IgM syndrome.

DIFFERENTIAL DIAGNOSIS: AIDS; X-linked agammaglobulinemia; Combined variable immunodeficiency (CVID).

SYMPTOMS AND SIGNS: As with most primary immunodeficiencies, recalcitrant infections occur early in life. However, unlike X-linked agammaglobulinemia, lymphoid hyperplasia is common and, although bacterial infections predominate, *Pneumocystis carinii* pneumonia may be the initial presenting infection. Gastrointestinal infections and malabsorption are common and occasionally severe. Neutropenia is commonly observed. The X-linked form of the disease may be associated with persistent stomatitis or oral ulcers. Bacterial cholangitis may be a life-threatening complication. Autoimmune cytopenias and thyroid disease can be seen, and anemia associated with chronic Parvovirus B19 infection has been re-

ported. Arthritis and malignancies also occur with increased frequency in these patients.

ETIOLOGY/EPIDEMIOLOGY: X-linked transmission is most common; therefore, most cases occur in males. The occurrence of the disease in women suggests autosomal-recessive or -dominant inheritance in some cases. In the X-linked form, the defect lies in the T cell, which fails to express the activation protein, CD40 ligand, necessary for signaling B-lymphocytes to switch production from IgM to other immunoglobulin types. Rarely, it may be the failure of the B-lymphocyte (CD40 receptor defect) to appropriately receive the T-cell signal.

DIAGNOSIS: Serum IgG and IgA are markedly decreased with concomitant normal or elevated levels of serum IgM (polyclonal elevation). Neutropenia occurs in more than 50% of patients, and anemia is common. Peripheral B-lymphocyte numbers are normal, but T cells characteristically fail to express CD40 ligand on their surfaces. Antibody function of the non-IgM classes is diminished. More than 20 separate point mutations that cause CD40 ligand to be defectively expressed have been described.

TREATMENT

Standard Therapies: As with other hypogammaglobulinemias, infusion of intravenous immune globulin (IVIG)

at 400 mg/kg/dose every 3–4 weeks results in a marked decrease in infections. Trough levels of serum IgG are maintained above 500 mg/dL. IgM levels may normalize and, in some cases, neutropenia may improve, but persistent cases require granulocyte colony-stimulating factor. In some cases, malabsorption may be severe, requiring total parenteral nutrition. Infants are especially prone to *Pneumocystis* pneumonia, mandating trimethoprim-sulfamethoxazole prophylaxis. All patients with anemia should be evaluated for parvovirus B19 infection by polymerase chain reaction and treated with high-dose IVIG 2,000 mg/kg divided over 1–2 days. Sclerosing cholangitis is a major complication requiring subspecialty management.

Investigational Therapies: Studies evaluating agents that activate the B-cell CD40 receptor are ongoing. Gene therapy is also being investigated.

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38 Large Granular Lymphocyte Leukemia

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DEFINITION: Large granular lymphocyte (LGL) leukemia is a chronic disorder characterized by clonal large granular lymphocytes.

SYNONYMS: LGL lymphoproliferative disease (LGL-LPD); T-cell chronic lymphocytic leukemia; Chronic T-cell lymphocytosis; T-suppressor cell leukemia; T-lymphoproliferative disease.

DIFFERENTIAL DIAGNOSIS: Other low-grade lymphoproliferative disorders; Reactive lymphocytosis; Viral infections.

SYMPTOMS AND SIGNS: Patients with LGL leukemia may present with a combination of fatigue and constitutional symptoms, cytopenias, hepatosplenomegaly, and bone marrow infiltration. Approximately one fourth of patients are asymptomatic at diagnosis. Anemia is noted in half of patients. Oval macrocytosis is present in some patients. Severe neutropenia (<500/mL) may be noted and may be associated with recurrent infections and mouth sores. Thrombocytopenia may be present and is generally mild. Patients with LGL lymphoproliferative disorders frequently have humoral immune abnormalities, including positive test results for rheumatoid factor, antinuclear antibodies, and polyclonal hypergammaglobulinemia. Rheu-

matoid arthritis, vasculitic syndromes, or splenomegaly may also be present.

ETIOLOGY/EPIDEMIOLOGY: The mean age at diagnosis is 60 years, with a slight male gender predilection. The cause is unknown, but findings from various studies suggest that a retrovirus or homologous protein may be implicated in the pathogenesis of the disease.

DIAGNOSIS: Diagnosis depends on the combination of the described clinical features, supported by blood cell morphology, immunophenotyping, and gene rearrangement studies. The diagnosis should be considered in patients with chronic or cyclic neutropenia, pure red cell aplasia, or rheumatoid arthritis associated with increased numbers of LGL cells. A substantial proportion of patients do not have elevated total lymphocyte counts and patients with less than 2000 LGL/ μ L (the traditional threshold for diagnosis) may have disease requiring therapy. Flow cytometry in conjunction with morphology is helpful in making the diagnosis of LGL leukemia.

TREATMENT

Standard Therapies: Individualization of therapy is particularly important in this disorder. Therapy is often supportive. Significant cytopenias as a result of pure red cell aplasia, hemolysis, or multilineage aplasia may warrant specific therapy. Additional indications for therapy may include neutropenia with recurrent infections, symptomatic splenomegaly, or rheumatoid arthritis. If evidence of signif-

icant hemolysis exists, corticosteroids may be the intervention of choice. In patients with pancytopenia, immunosuppression with antithymocyte globulin or cyclosporine may be helpful. Cyclophosphamide may also be useful, particularly in patients with pure red cell aplasia, as it can reduce the long-term toxicity of chronic corticosteroid therapy.

Investigational Therapies: Methotrexate is being investigated.

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39 Lymphangioleiomyomatosis

**Arnold S. Kristof, MD, FRCPC,
and Joel Moss, MD, PhD**

DEFINITION: Lymphangioleiomyomatosis (LAM) is a disease of abnormal smooth muscle proliferation in the lung, abdominal organs, and axial lymphatics. It occurs primarily in women of childbearing age and involves the formation of abdominal angiomyolipomas as well as cystic pulmonary lesions that cause recurrent pneumothoraces and chronic respiratory failure.

DIFFERENTIAL DIAGNOSIS: Tuberous sclerosis complex; Emphysema; Eosinophilic granuloma; Sarcoidosis; Diffuse pulmonary lymphangiomatosis; Cystic fibrosis; Asthma.

SYMPTOMS AND SIGNS: LAM is most often diagnosed in patients who present with progressive dyspnea or recurrent pneumothoraces. Patients may experience chronic cough, wheezing, and hemoptysis, as well as symptoms related to chylous ascites or pleural effusions. Angiomyolipomas and axial lymphatic masses, which frequently involve the kidneys, may give rise to flank pain, hematuria, and, rarely, abdominal hemorrhage. Engorgement of the lymphatics (e.g., lymphangioleiomyoma) can result in lower extremity swelling. Physical examination of the lung most commonly shows crackles; wheezing occurs in some patients. Dullness to percussion and decreased breath sounds are present in patients with chylothorax. Abdominal masses may be palpated in patients with angiomyolipomas and lymphangioleiomyomas.

ETIOLOGY/EPIDEMIOLOGY: Approximately 400 cases of LAM are reported in the United States; the true incidence is unknown. Lung cysts characteristic of LAM occur in approximately 30% of patients with tuberous sclerosis complex (TSC), suggesting a common etiology. Unlike TSC, LAM is not inherited, and specific genetic mutations have not been described.

DIAGNOSIS: Characteristic thin-walled cysts seen on high-resolution chest CT are consistent with LAM. Angiomyolipomas seen on abdominal imaging support the diagnosis. The gold standard is open lung, transbronchial, or angiomyolipoma biopsy with histopathologic evidence of proliferation of abnormal smooth muscle cells that are immunoreactive with a monoclonal antibody, HMB45. Chest radiography shows increased interstitial markings with preserved lung volumes. Pulmonary function testing demonstrates an obstructive ventilatory abnormality with superimposed restriction in 20% of patients. A significant bronchodilator response may be detected in 25% of patients. The diffusion capacity is commonly decreased disproportionately to abnormalities in spirometry or lung volumes, and correlates inversely with disease severity.

TREATMENT

Standard Therapies: Dyspnea and cough are treated symptomatically. Patients with a significant bronchodilator response on pulmonary function testing may benefit from inhaled bronchodilators and/or corticosteroids. Supplemental oxygen should be administered as required. Recurrent pneumothorax and chylous effusions may warrant chemical pleurodesis. The use of talc should be avoided, because patients may ultimately require lung transplantation.

Reduced dietary intake of triglycerides in patients with chylous effusions has not been shown to be beneficial. Because LAM is strongly associated with osteoporosis, bone density should be measured in all patients, and any bone density loss should be treated aggressively with bisphosphonates in conjunction with calcium and vitamin D supplementation. Surgical resection of abdominal angiomyolipomas should be considered in patients with unrelenting pain or hemorrhage. Because LAM occurs primarily in women of child-bearing age, the mainstay of treatment has been the use of agents or procedures that reduce estrogen levels. No controlled trials have shown that exogenous progesterone, androgens, or bilateral oophorectomy have an effect on survival or preservation of lung function.

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40 Hereditary Lymphedema

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DEFINITION: Hereditary (primary) lymphedema is developmental dysplasia of the lymph circulatory system, resulting in the accumulation of protein-rich fluid in the interstitium and peripheral edema.

SYNONYMS: Nonne-Milroy disease or congenital lymphedema; Meige disease or lymphedema praecox (if onset is before age 35); Lymphedema tarda (onset after age 35).

DIFFERENTIAL DIAGNOSIS: Lipedema; Venous insufficiency; Phlebothrombosis; Myxedema; Tumor obstructing lymph flow.

SYMPTOMS AND SIGNS: Signs include swelling of all or a segment of a limb, usually unilateral. Hereditary lymphedema usually is first noticed distally but can involve the adjacent trunk, including the genitalia. Congenital lymphedema is present at birth and can affect more than one limb and the face. Meige disease usually occurs around the time of puberty and onset can be gradual or sudden. Trauma, infection, or pregnancy can precipitate the edema. Pitting edema may be present in early, nonfibrotic lymphedema. Chronic lymphedema is nonpitting and fibrotic with thickened cutaneous folds. Stemmer sign may be present. The patient may have limb tightness, heaviness, and restricted joint movement.

ETIOLOGY/EPIDEMIOLOGY: Hereditary lymphedema can be inherited in different ways. Milroy and Meige diseases are familial and dominantly inherited in some families. A lymphedema gene has been localized to the bottom

of human chromosome 5 (vascular endothelial growth factor–C receptor). Four other lymphedema-causing genetic changes have been identified. The estimated occurrence of primary lymphedema is 1 in 6,000. The distribution is reported to be 87% in women and 13% in men. Associated developmental disorders may include Klippel-Trenaunay-Weber syndrome, Turner XO syndrome, Noonan syndrome, and lymphedema-hypoparathyroid syndrome. Lymphostatic enteropathy due to intestinal lymphangiectasis has been observed with Noonan syndrome and Nonne-Milroy disease.

DIAGNOSIS: The history and physical examination usually confirm the diagnosis. Lymphoscintigraphy is the imaging examination of choice. Direct lymphography is invasive and rarely used due to complications caused by the contrast agent. Venous ultrasonography or venography can rule out phlebothrombosis as the cause of limb edema. MRI can detect tissue edema, lymphoceles, and fibrosis.

TREATMENT

Standard Therapies: Complex decongestive therapy is the preferred treatment for lymphedema. It includes manual lymph decongestive massage, compression bandaging with short stretch elastic bandages, exercises, and instruction in self-care. Sequential intermittent compression pumps are used occasionally to treat nonfibrotic lymphedema and never as the sole modality of treatment. Rehabilitation therapy is necessary in cases of severe lymphedema resulting in impairment of the activities of daily living. Peripheral lymphedema is more severe in overweight individuals; they should follow a reducing diet and exercise program. Diuretics can be of short-term benefit in early, nonfibrotic lymphedema, but cause concentration of os-

motically active interstitial proteins and, in the long term, aggravate lymphedema. Emotional support should be available to patients because they may experience embarrassment, anger, anxiety, and depression. Surgical treatment—debulking or microlymphatic anastomoses—is rarely effective.

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41 Hemophagocytic Lymphohistiocytosis

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DEFINITION: Hemophagocytic lymphohistiocytosis (HLH) is an aggressive proliferation of macrophages that causes fevers, organomegaly, pancytopenia, coagulopathy, liver failure, and central nervous system symptoms.

SYNONYMS: Familial hemophagocytic lymphohistiocytosis; Familial erythrophagocytic lymphohistiocytosis; Viral-associated hemophagocytic syndrome.

DIFFERENTIAL DIAGNOSIS: Sepsis; Leukemia; Fever of unknown origin.

SYMPTOMS AND SIGNS: Patients present with high fevers, maculopapular rash, failure to thrive, hepatosplenomegaly, lymphadenopathy, cytopenias, coagulopathy, elevated liver function test results, and high serum ferritin.

ETIOLOGY/EPIDEMIOLOGY: The disease most often affects infants from birth to 18 months, but older children and adults are also affected. In Sweden, the incidence is estimated to be 1.2 children per million per year or 1 in 50,000 live births. The male:female ratio is nearly equal. It is likely that many children go undiagnosed. Among the infections associated with HLH are Epstein-Barr virus, cytomegalovirus, parvovirus, herpes simplex, varicella-zoster virus, and measles, fungal and bacterial. HLH has been found in patients with lupus, arthritis, immune deficiencies, and malignancies. Familial cases may represent as many as 50% of all cases and are frequently associated with parental consanguinity. There is no way to distinguish between familial or sporadic cases based on any laboratory test or clinical feature. Markedly elevated levels of several cytokines in the blood cause HLH. Among these are inter-

feron- γ , tumor necrosis factor- α , interleukin-10, and interleukin-12, as well as elevated levels of interleukin-2 receptor. Patients have markedly decreased or absent natural killer cell function and the test serves as a surrogate marker for disease susceptibility. Natural killer dysfunction is associated with a defect in the perforin gene on chromosome 10. The connection between these defects and the disease is still being investigated.

DIAGNOSIS: Specific criteria for diagnosis include the following: fever, peaks above 38.5 °C for 7 days or more; splenomegaly, more than 3 cm below costal margin; cytopenias affecting two or more lineages; hemoglobin less than 90 g/L; platelets less than 100×10^9 /L; neutrophils less than 1.0×10^9 /L; coagulopathy with markedly prolonged prothrombin time/partial thromboplastin time; fibrinogen less than 1.5 g/L or less than 3 SD; and hypertriglyceridemia (fasting level greater than 2 mM) and/or hyperferritinemia ($>1,000$ ng/mL). The key diagnostic finding, hemophagocytosis by macrophages in the bone marrow, lymph nodes, or spleen, is present in 80% of patients.

TREATMENT

Standard Therapies: Treatment by the Histiocyte Society HLH-94 protocol includes induction with dexamethasone and etoposide (VP-16), followed by continuous cyclosporine with pulses of dexamethasone and VP-16 for 1 year. This therapy may be sufficient for children older than 4 years, but bone marrow transplantation provides the best overall cure rate, above 60%. It is critical that all patients be registered on this protocol so advances in the cure and understanding of HLH can be made. Use of immunosuppressive agents, antiviral drugs, or steroids alone have not been as successful as the HLH-94 protocol, and the use of these is discouraged.

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42 Angioimmunoblastic Lymphadenopathy-Type T-Cell Lymphoma

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DEFINITION: Angioimmunoblastic T-cell lymphoma (AIL) is a subtype of peripheral T-cell non-Hodgkin lymphoma (NHL). Characteristic presenting features include generalized, low-volume lymphadenopathy, hepatosplenomegaly, skin rashes, and polyclonal hypergammaglobulinemia, associated with marked constitutional symptoms including fevers, night sweats, and arthralgias.

SYNONYMS: Angioimmunoblastic lymphadenopathy with dysproteinemia; Immunoblastic lymphadenopathy; Lymphogranulomatosis X.

DIFFERENTIAL DIAGNOSIS: Other forms of NHL, particularly indolent lymphomas and primary cutaneous T-cell lymphoma.

SYMPTOMS AND SIGNS: The median age of onset is approximately 60–65 years. Typical presenting symptoms include marked constitutional symptoms such as night sweats, fevers, and weight loss. A history of generalized pruritis and pruritic skin rashes is common. Other common presenting symptoms include lymphadenopathy, which is usually low volume, hepatosplenomegaly, the presence of pleural effusions, ascites, peripheral edema, and a polyclonal hypergammaglobulinemia. Mediastinal lymphadenopathy is common. Autoimmune phenomena such as mild arthritis, Coombs-positive hemolytic anemia, rheumatoid factor, cryoglobulins, and circulating immune complexes are also common. Most patients have stage III or IV disease at presentation.

ETIOLOGY/EPIDEMIOLOGY: The disorder is a subtype of NHL, constituting less than 1% of all cases. The etiology is unknown, although an association with Epstein-Barr virus has been reported.

DIAGNOSIS: The diagnosis of AIL is made by biopsy of an affected lymph node or involved extranodal site.

TREATMENT

Standard Therapies: Optimal therapy is poorly defined. Various approaches have included the use of corticosteroids alone, single-agent chemotherapy, and multiagent combination chemotherapy. The most widely reported chemotherapy regimen is COPBLAM/IMVP16 (cyclophosphamide, vincristine, bleomycin, adriamycin, procarbazine, prednisone, ifosfamide, methotrexate, etoposide). Reported median overall survivals for patients with AIL are between 6 and 18 months. Long-term (>5 years) disease-free survival is reported in only 20%–30% of patients.

Investigational Therapies: Experimental therapies have included cyclosporine A and interferon.

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RESOURCES

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43 Mantle Cell Lymphoma

Jorge Romaguera, MD

DEFINITION: Mantle cell lymphoma is an uncontrolled growth of lymphocytes that normally reside in the mantle zone of the germinal follicle.

DIFFERENTIAL DIAGNOSIS: Follicular indolent lymphoma; Small lymphocytic lymphoma.

SYMPTOMS AND SIGNS: Signs of mantle cell lymphoma include enlarged nodes in the neck and groin and under the arms. Drenching sweats, fevers, more than 10% weight loss, diarrhea, gastrointestinal bleeding, or abdominal pain occur in 10% of patients.

ETIOLOGY/EPIDEMIOLOGY: Mantle cell lymphoma accounts for 8% of all non-Hodgkin lymphomas. It occurs more frequently in males, by a 3:1 ratio. The median age at diagnosis is 61 years. In 90%–100% of patients, the disease is in the advanced stages at presentation. The cause is not known.

DIAGNOSIS: Biopsy of enlarged lymph nodes is strongly recommended. Nodal distribution of the characteristic cell can be nodular or diffuse. This cell is of intermediate size and stains positive for CD5/CD19 (coexpression) and FMC-7, but negative for CD23. A chromosomal translocation juxtaposes the cyclin D1 oncogene located on 11q23 to the active 14q32 area and overproduces the cyclin D1 protein (a cell cycle regulator). Cyclin D1 immunohistochemical stains are positive.

TREATMENT

Standard Therapies: There are no standard therapies. Response to cyclophosphamide, doxorubicin, vincristine, and

prednisone is poor. The complete response rate is 21%, with the median duration of response 10 months, and median survival 3 years. Autologous stem cell transplantation is not effective as salvage therapy. The best responses have been seen with aggressive, intense frontline chemotherapy with high-dose cyclophosphamide, total body irradiation, and autologous stem cell transplantation (100% complete response, 73% event-free survival at 2 years). The best results for relapsed/resistant disease are achieved with intense chemotherapy followed by allogeneic stem cell transplantation. Monoclonal antibody therapy seems to be effective and promising.

Investigational Therapies: For initial therapy, fractionated cyclophosphamide, doxorubicin, vincristine, and dexamethasone, alternating with high-dose methotrexate/cytarabine and rituximab in each cycle, are being investigated. For patients who have relapsed, allogeneic stem cell transplantation with nonmyeloblastic chemotherapy is being studied.

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RESOURCES

241, 251, 352

44 X-Linked Lymphoproliferative Syndrome

Roger H. Kobayashi, MD

DEFINITION: X-linked lymphoproliferative (XLP) syndrome is an X-linked disease in which young males are exquisitely susceptible to overwhelming Epstein-Barr virus (EBV) infections.

SYNONYMS: Duncan disease; Purtilo syndrome; Fatal infectious mononucleosis syndrome.

DIFFERENTIAL DIAGNOSIS: Hypogammaglobulinemia; Malignant lymphoma; Aplastic anemia; Hemophagocytic syndrome.

SYMPTOMS AND SIGNS: Patients appear normal until they contract EBV infection, developing one or more of the following manifestations: fatal infectious mononucleosis, malignant lymphoma, hypogammaglobulinemia, or aplastic anemia. In the fulminant infectious mononucleosis form, high fever, massive hepatosplenomegaly, elevated white cell count with atypical lymphocytosis, and elevated immunoglobulins are presenting findings. As the disease rapidly progresses, pancytopenia with massive bone marrow infiltration ensues. Those who survive develop lymphoma, bone marrow failure, or combined immunodeficiency. Virtually all patients die, and no patient has survived past 40 years of age. Just before death, marrow failure and histiocytic hemophagocytosis are seen. As many as one third of patients may present with hypogammaglobulinemia before EBV infection. Rarely, lymphoma, agammaglobulinemia, or aplastic anemia may be the initial presenting feature.

ETIOLOGY/EPIDEMIOLOGY: XLP disease occurs from a defect in the *SH2D1A* gene located at Xq25 of the long arm of the X chromosome. This gene encodes for a small protein that may be important in signal transduction in activated T-lymphocytes. This defect allows for uncontrolled proliferation of EBV-infected B cells.

DIAGNOSIS: The clinical diagnosis depends on characteristic findings, together with a positive family history. A positive family history includes two or more maternally related males with XLP presentation after an EBV infection or a maternally-related male from an XLP family with ge-

netic linkage to the XLP locus. A positive family history with low serum IgG and/or elevated IgA or IgM is suggestive but requires genetic studies. Absent or poor anti-EBNA response after EBV infection is also suspicious and should be followed up with genetic studies. Similarly, findings of histiocytic hemophagocytosis after EBV infection warrant genetic evaluation.

TREATMENT

Standard Therapies: Treatment is with histocompatible bone marrow transplantation. High-dose intravenous immune globulin (IVIG) together with interferon- α or interferon- γ have been tried in the fulminant phase with poor results. High-dose IVIG or methylprednisolone together with VP-16 (etoposide) have been used successfully in several children with the fulminant form, allowing for subsequent bone marrow transplantation. In XLP-identified patients without prior EBV infection, IVIG has been used prophylactically; the benefits are unproven, however, because several patients subsequently developed overwhelming EBV infection and died.

Investigational Therapies: Prophylaxis with EBV vaccine has been considered.

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RESOURCES

193, 352, 359

45 Lynch Syndromes

Henry T. Lynch, MD

DEFINITION: Lynch syndromes I and II account for approximately 5%–8% of all colorectal cancer (CRC) patients. Lynch syndrome I is an autosomal-dominantly inherited disease that predisposes to site-specific CRC with an early age of onset (~44 years), proximal predominant location of CRC (~70% proximal to the splenic flexure), and a statistically significant excess of synchronous and metachronous CRCs. Lynch syndrome II shows these same features but, in addition to CRC, there is a statistically significant excess of carcinomas of the endometrium, ovary, stomach, small bowel, hepatobiliary system, and transitional cell carcinomas of the ureter and renal pelvis. Sebaceous adenomas and carcinomas and multiple keratoacanthomas occur in the Muir-Torre syndrome variant.

SYNONYM: Hereditary nonpolyposis colorectal cancer (HNPCC).

DIFFERENTIAL DIAGNOSIS: All diseases associated with hereditary CRC. Familial adenomatous polyposis (FAP) can be excluded because of its profuse colonic adenomas, but the attenuated variant of FAP with an *APC* germline mutation is included. Other related disorders include: Familial CRC clusters; Hereditary hamartomatous polyposis syndromes; Ashkenazi *11307K* mutation; Turcot syndrome; Familial CRC; Inflammatory bowel disease.

SYMPTOMS AND SIGNS: Symptoms and signs are those of each Lynch syndrome cancer. Pathology findings of CRC show a tendency toward a solid growth pattern, which accounts for the high frequency of poorly differentiated carcinomas, wherein these tumors resemble the “undifferentiated carcinoma” and the “medullary carcinoma” that have been described. These tumors appear to have a better prognosis than more typical types of CRC. Tumors contain the host-lymphoid response, namely, the Crohn-like reaction, peritumoral lymphocytic infiltrations, and tumor-infiltrating lymphocytes.

ETIOLOGY/EPIDEMIOLOGY: Causal germline mutations have been implicated in the DNA mismatch repair genes *MLH1*, *MSH2*, *MSH6*, *PMS1*, and *PMS2*, the most common being *MLH1* and *MSH2*. All racial and ethnic groups are at risk.

DIAGNOSIS: The syndrome should be suspected in patients with early age of onset of CRC and the integral cancers in the Lynch syndrome II variant, particularly when these appear to cluster within first- and second-degree relatives of the affected proband (revised Amsterdam criteria). An annual colonoscopy (because of accelerated carcinogenesis) is indicated because of excess of proximal CRC, in which a third of these tumors occur in the cecum. Screening for carcinoma of the endometrium includes transvaginal ultrasonography of the endometrium and the ovaries, endometrial aspiration, and CA 125 for ovaries. Ovarian screening has limitations, however.

TREATMENT

Standard Therapy: Standard therapy for CRC and integrally associated cancers is usually undertaken. Because of lifetime vulnerability of the entire colonic mucosa, a subtotal colectomy for initial CRC is recommended, with annual endoscopic evaluation of the remaining rectal-sigmoid area. Prophylactic colectomy is an option, particularly for carriers of mismatch repair gene mutations with early adenoma occurrence, poor compliance for full colonoscopy, or intense fear of CRC. Prophylactic hysterectomy and bilateral salpingo-oophorectomy is an option for women with germline mutations who have completed their families.

Investigational Therapies: Chemoprevention, including celecoxib, is being studied.

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46 Mastocytosis

**Cem Akin, MD, PhD,
and Dean D. Metcalfe, MD**

DEFINITION: Mastocytosis is characterized by the presence of increased numbers of mast cells in tissues, most commonly in the skin, bone marrow, spleen, liver, lymph nodes, and the gastrointestinal tract.

DIFFERENTIAL DIAGNOSIS: Idiopathic flushing, angioedema and/or anaphylaxis; Carcinoid syndrome; Pheochromocytoma; Leukemias; Lymphomas; Reactive mast cell hyperplasia.

SYMPTOMS AND SIGNS: Whereas cutaneous mastocytosis is the most common presentation in children, systemic (bone marrow) involvement is often encountered in adult-onset disease. Urticaria pigmentosa is the most common skin manifestation. The lesions may be pruritic. Infants and young children may experience idiopathic bullous eruptions over involved areas. Less common patterns of skin disease include diffuse cutaneous mastocytosis, telangiectasia macularis eruptive perstans, and mastocytomas. Most patients, in addition to the skin lesions, may variably demonstrate one of the following findings: ulcer disease, malabsorption, diarrhea, bone marrow pathology (mast cell aggregates), osteoporosis or osteosclerosis, hepatosplenomegaly, lymphadenopathy, soft tissue pain, fatigue, flushing and systemic anaphylaxis. Some forms of mastocytosis may be associated with a hematologic disorder such as myelodysplastic syndromes or myeloproliferative disorders. Mast cell leukemia is rare and is diagnosed by the presence of large numbers of mast cells in the peripheral blood.

ETIOLOGY/EPIDEMIOLOGY: Mastocytosis affects approximately equal numbers of males and females. The disease can occur at any age, although childhood-onset disease usually starts before age 6 months. Adult-onset mastocytosis appears to be a clonal neoplastic disorder of the hematopoietic stem cell. Somatic gain-of-function mutations in *c-kit*, the gene encoding the receptor for stem cell factor, have been detected in lesional skin in most adult patients and a few children. The cause of most cases of typical childhood-onset mastocytosis is unknown.

DIAGNOSIS: The diagnosis is suspected based on the presence of typical skin lesions and confirmed by biopsy. In

some individuals with no skin lesions, a bone marrow biopsy demonstrating characteristic mast cell aggregates surrounded by a mononuclear infiltrate is diagnostic. Bone marrow biopsy and aspirate is recommended for patients with adult-onset disease and for children only if they have hepatosplenomegaly, lymphadenopathy, or peripheral blood abnormalities. Flow cytometric analysis of the bone marrow aspirate shows mast cells with surface CD2 and CD25 in most patients with systemic mastocytosis. A complete blood count, routine chemistry, liver function, and coagulation tests should be obtained in virtually every patient. An elevated baseline serum or plasma tryptase level (usually >20 ng/mL), considered to be a surrogate marker of total body mast cell numbers, may be helpful in diagnostic evaluation.

TREATMENT

Standard Therapies: Management of mastocytosis is aimed at controlling symptoms. H1 histamine receptor blockers are used to reduce pruritus and flushing. H2 antihistamines are useful in controlling symptoms due to gastric acid hypersecretion. Oral cromolyn sodium may help lessen gastrointestinal pain and cramping. Corticosteroids are used to control symptoms such as diarrhea with malabsorption and ascites. Topical corticosteroids or psoralen-UV-A treatment may result in temporary fading of the urticaria pigmentosa lesions. Epinephrine is used to treat episodes of vascular collapse. Patients with mastocytosis and an associated hematologic disorder should be treated for the specific hematologic disease. Interferon- α 2b has been used with mixed success in patients with advanced bone marrow mastocytosis.

Investigational Therapies: Therapies under investigation include bone marrow transplantation and the use of tyrosine kinase inhibitors, targeting the mutated *c-kit* gene product.

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RESOURCES

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47 May-Hegglin Anomaly

Michael J. Kelley, MD

DEFINITION: May-Hegglin anomaly is an inherited platelet condition characterized by thrombocytopenia, giant platelets, and leukocyte inclusions.

SYNONYM: Macrothrombocytopenia with leukocyte inclusions.

DIFFERENTIAL DIAGNOSIS: Sebastian syndrome; Idiopathic thrombocytopenia; Fechtner syndrome; Epstein syndrome; Bernard-Soulier syndrome; Gray platelet syndrome.

SYMPTOMS AND SIGNS: May-Hegglin anomaly is usually discovered incidentally when a platelet count is performed. Bleeding complications are generally mild. Approximately one third to one half of patients have symptoms including easy bruising, hypermenorrhagia, and postoperative hemorrhage. Exsanguination has not been reported. Many persons with the anomaly have had normal childbirth and surgery without complications. There are no distinctive physical findings.

ETIOLOGY/EPIDEMIOLOGY: May-Hegglin anomaly is inherited as an autosomal-dominant condition. The disorder is associated with mutations of the nonmuscle myosin heavy-chain type A (MYH9) gene on chromosome 22q. Prevalence is estimated at approximately 1 in 500,000. The anomaly is increasingly recognized since the widespread availability of electronic particle counters for automated platelet counting. May-Hegglin anomaly occurs in most caucasian and Asian ethnic groups, but rarely, if at all, in Africans. The features of May-Hegglin anomaly are present at birth.

DIAGNOSIS: Clinically, the platelet count is usually 40,000–80,000/ μ L but can be as low as 5,000/ μ L or nearly normal. The platelet number is underestimated by counting in electronic particle counters compared with manual

counting using a hemocytometer, because many platelets may be above the size cutoff used for platelets. The mean platelet volume is usually greater than normal but can be normal if the electronic particle counter does not count the larger platelets. Hemoglobin indices and leukocyte count are normal. The peripheral blood smear is characteristic for giant platelets, large platelets, low to normal platelet estimate, and large distinctive azurphilic inclusions in leukocytes. Normal renal and auditory functions are typical and distinguish May-Hegglin anomaly from Fechtner and Epstein syndrome. Each neutrophil typically has at least one inclusion, as do many of the other granulocytes and monocytes. Immunohistochemical analysis of peripheral blood smears may show altered localization of nonmuscle myosin heavy-chain type A. Toxic granulations are absent. Bleeding time, platelet aggregation studies, and coagulation studies are normal. Ultrastructural analysis of leukocytes by electron microscopy shows the inclusions to be parallel bundles of filaments with characteristics of intermediate filaments. Genetic analysis is possible; penetrance is apparently complete with no phenocopies other than Sebastian syndrome, which is identical except for variant leukocyte inclusions.

TREATMENT

Standard Therapies: Most patients require no treatment and have normal life spans. For patients with significant hemorrhage, platelet transfusions are the treatment of choice. Other etiologies for hemorrhage should be considered. Treatment with corticosteroids, immunoglobulins, and splenectomy has not been effective.

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RESOURCES

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48 Medulloblastoma

Corey Raffel, MD, PhD

DEFINITION: Medulloblastoma is a rapidly growing tumor, made up of small round cells with little cytoplasm, which occurs in the cerebellum of children. Mitotic activity is high and neuroblastic or glial differentiation may be seen.

SYNONYM: Primitive neuroectodermal tumor (PNET).

DIFFERENTIAL DIAGNOSIS: Ependymoma; Pilocytic astrocytoma; Astrocytoma; Choroid plexus papilloma; Choroid plexus carcinoma.

SYMPTOMS AND SIGNS: Symptoms often include those of raised intracranial pressure. Because the tumor often fills the fourth ventricle, cerebrospinal fluid circulation is obstructed and hydrocephalus results. Symptoms of elevated intracranial pressure include headache, vomiting, and, less often, diplopia. Signs of elevated intracranial pressure include papilledema and paresis of extraocular muscles. Children with medulloblastoma often have evidence of cerebellar dysfunction. Symptoms include difficulty walking and poor balance. Signs include truncal ataxia and, less often, appendicular ataxia. In infants the only sign may be an abnormally rapid rate of head growth. Rarely, a patient will present obtunded, from severe hydrocephalus.

ETIOLOGY/EPIDEMIOLOGY: The cause is unknown. The tumor occurs most often in children (80% of patients are younger than 15 years of age), with a median age at diagnosis of 6 years. It is more common in boys than girls, with a 2:1 male predominance. The incidence is approximately 5 cases per million population younger than 15 years.

DIAGNOSIS: The diagnosis of medulloblastoma should be considered in any child with the symptoms and signs previously mentioned. Workup includes MRI of the head before and after administration of gadolinium-based contrast material. The tumor appears as a bright, contrast-enhancing mass that arises in the roof of the fourth ven-

tricle and usually fills the ventricle. The enhancement is usually homogeneous. There may be cystic areas in the tumor. If MRI is unavailable, CT before and after the administration of intravenous iodine-based contrast material may be used. On CT, the mass appears to attenuate radiographs more than the surrounding cerebellum. Again, contrast enhancement is usually bright and relatively homogeneous. If the patient is not severely obtunded from hydrocephalus, MRI of the entire spine should also be performed to look for cerebrospinal fluid dissemination of the tumor.

TREATMENT

Standard Therapies: Standard therapy for medulloblastoma includes surgical resection and radiation therapy. Gross total removal of tumor improves outcome; however, if the tumor is invading the floor of the fourth ventricle, it should be left in place, because attempted removal virtually guarantees severe neurologic sequelae. Adjuvant radiation therapy is usually given in 180 rad fractions. A total dose of 3,600 rad to the neuraxis with a tumor boost to 5,400 rad is standard. Because the effects of craniospinal radiation therapy to the child's brain are devastating, chemotherapy has been added in an attempt to decrease the dose of irradiation. Platinum-based chemotherapy has been shown to improve the outcome in children with high-risk disease. Five-year survival for optimally treated normal-risk patients is approximately 65%; for optimally treated high-risk patients, 5-year survival is less than 20%.

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RESOURCES

30, 290, 352

49 Melanoma

Jonathan J. Lewis, MD, PhD

DEFINITION: Melanoma is a type of skin cancer that results from the malignant transformation of the normal melanocytes or pigment cells found in the skin.

DIFFERENTIAL DIAGNOSIS: Benign nevus; Dysplastic mole; Seborrheic keratoses; Squamous and basal carcinoma.

SYMPTOMS AND SIGNS: Patients usually present with a pigmented lesion of the skin that has undergone recent change. These lesions typically have irregular borders, an irregular surface, and irregular colors, which may range from pink to blue to brown to black. Late symptoms may include itchiness and bleeding. Any of these changes in a nevus is a sign that it may be undergoing a malignant transformation. In 5%–10% of cases, melanoma arises from other sites, including the oral cavities, nasal sinuses, genitalia, and rectum. Melanoma may also occur in the uveal tract and the retina of the eye. In all these sites, it presents as a pigmented lesion.

ETIOLOGY/EPIDEMIOLOGY: Individuals of Celtic ancestry have the highest risk for developing melanoma. Men develop melanoma slightly more frequently than women. In women, melanomas occur more commonly on the lower extremities, whereas in men they occur more commonly on the trunk, head, and neck. A primary cause of melanoma is believed to be sun exposure, and that both UVA and UVB are carcinogenic. At highest risk are people with fair complexions who have had intermittent sun exposure and a history of severe sunburns. The incidence of melanoma in the United States is 40,000 per year, of whom 7,400 will die from it.

DIAGNOSIS: Careful and thorough examination of the skin is crucial. Any pigmented lesion that is irregular or that has a diameter of more than 6 mm and elevation should arouse suspicion. To make the diagnosis, a full-thickness biopsy should be performed. An excisional biopsy can be done on small lesions, whereas for large lesions a punch biopsy through the representative area or areas can be performed. A shave biopsy should not be

done, as it does not allow adequate assessment of the depth of the lesion, which is crucial in diagnosis and staging. The diagnosis is then based on examination under the microscope, best done by a dermatopathologist. Once the diagnosis is established, careful examination and evaluation of the draining lymph nodes and other sites of metastases should be performed.

TREATMENT

Standard Therapies: Standard treatment is a wide local excision. When indicated, a sentinel lymph node biopsy should be performed; most appropriately in patients with intermediate-thickness melanomas. Systemic therapy in the adjuvant setting for high-risk lesions can be useful. One current standard of care includes the use of interferon. Once metastatic, several systemic agents may be used, including the chemotherapy agent dacarbazine and the biologic agent interleukin-2.

Investigational Therapies: Vaccines are being evaluated; different approaches include some that use the antibody arm and others that use the T cell arm of the immune system.

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RESOURCES

30, 352, 437

50 Mycosis Fungoides

John A. Zic, MD

DEFINITION: Mycosis fungoides is the most common variant of the primary cutaneous T-cell lymphomas, characterized by the indolent onset of red patches of skin in sun-protected areas, which may progress to thick plaques, tumors, and/or total body erythroderma.

SYNONYM: Mycosis fungoides of Alibert and Bazin.

DIFFERENTIAL DIAGNOSIS: Large plaque parapsoriasis; Adult T-cell leukemia/lymphoma; Sezary syndrome; Allergic contact dermatitis; Eczematous dermatitis; Psoriasis; Tinea corporis.

SYMPTOMS AND SIGNS: The classic presentation is a middle-aged to older adult with an asymptomatic eruption of large (>5 cm), pink to red, scaly flat patches on the thighs or buttocks of several years' duration. Often, the patient has been misdiagnosed with eczema or psoriasis. Low- to midpotency topical steroids stabilize the condition temporarily over a period of years. The patches ultimately evolve into thin elevated plaques. Skin biopsy shows an atypical lymphocytic infiltrate. On average, most patients have the eruption for 6–10 years before the diagnosis is established. Patients with less than 10% of their body surface covered with patches or plaques and no extracutaneous involvement have a normal life expectancy with treatment. Approximately 1 in 10 early-stage patients will progress to more advanced stages. Thick plaques may ulcerate, forming tumors, and total body erythema may evolve. Blood involvement is not uncommon in advanced patients. Regional peripheral lymphadenopathy is the most common extracutaneous finding, followed by metastasis to bone marrow, lung, and liver. Patients with large, often ulcerated, tumors or erythroderma have a poor prognosis, with a median survival of approximately 30 months. Most advanced-stage patients die of sepsis due to *Staphylococcus*.

ETIOLOGY/EPIDEMIOLOGY: The etiology and risk factors are unknown. One theory is that activated T cells destined for the skin undergo malignant transformation and proliferation. Approximately 1,000 new cases are diagnosed in the United States each year, and approximately

10,000 to 15,000 Americans are affected. The male:female ratio is 2:1, and twice as many blacks are diagnosed as whites.

DIAGNOSIS: Multiple punch biopsies of the skin are required to make the diagnosis. Pathologists experienced with the disease should evaluate the specimens. Occasionally, T-cell receptor gene rearrangement studies are helpful in establishing the diagnosis. Routine chemistries and a manual complete blood count and differential should be obtained. CT scans are helpful only in patients with tumors, erythroderma, or widespread disease.

TREATMENT

Standard Therapies: Patients in the early stage of disease with only skin involvement are treated with topical nitrogen mustard, topical carmustine, topical bexarotene gel, and phototherapy. Patients with progressive disease may be treated with psoralen-UVA phototherapy alone or with subcutaneous interferon, total skin or localized electron beam radiotherapy, oral bexarotene, photopheresis, and methotrexate. Patients in advanced stages may receive intravenous denileukin diftitox, single agent chemotherapy, and combination chemotherapy.

Investigational Therapies: Peripheral blood stem cell transplantation is being explored.

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RESOURCES

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51 Multiple Myeloma

Morie A. Gertz, MD

DEFINITION: Multiple myeloma is a malignancy of plasma cells that infiltrates the bone marrow. The clinical manifestations are bone disease characterized by lytic destruction, pathologic fractures, and diffuse osteoporosis. Anemia due to progressive bone marrow replacement is common, and patients may develop renal insufficiency related to the production of excessive immunoglobulin light chains, toxic to the renal tubules.

SYNONYMS: Plasma cell myeloma; Myeloma.

DIFFERENTIAL DIAGNOSIS: Metastatic malignancy to bone; Normochromic normocytic anemia; Renal insufficiency of an indeterminate origin.

SYMPTOMS AND SIGNS: The most common presenting symptoms are fatigue, due to anemia, secondary to progressive infiltration of the bone marrow, and bone pain. Typically, the pain involves the spine. Patients may have associated pathologic fractures of multiple ribs. Skeletal destruction may occur in any bone. Radiography of the calvarium generally demonstrates lytic lesions.

ETIOLOGY/EPIDEMIOLOGY: No specific etiology has been identified, although there is an increased incidence of multiple myeloma in individuals exposed to ionizing radiation. Only 1% of patients have such a history. No familial or inherited predisposition to this disorder has been recognized. The male:female ratio is 55:45. The incidence is 4 per 100,000 per year. The disease is seen in 13,800 patients per year in the United States and constitutes 1% of all cancer and 10% of hematologic cancers. It is twice as common in blacks as whites. The median age at diagnosis is 62 years.

DIAGNOSIS: The diagnosis requires bone marrow aspiration and biopsy demonstrating more than 10% plasma cells in the bone marrow. Appropriate staging procedures include a radiograph of the entire skeleton, searching for fractures or lytic disease. Laboratory testing includes measurement of hemoglobin, renal function, blood calcium

level, and uric acid. The hallmark of multiple myeloma is the detection of a monoclonal protein (M protein) in the serum or urine. The source of the protein is the malignant plasma cell in the bone marrow.

TREATMENT

Standard Therapies: Occasional patients will be diagnosed without symptoms present, and may be observed for the development of symptomatic disease. For patients with solitary plasmacytomas, radiation therapy suffices. For patients who cannot be treated with localized radiation, systemic chemotherapy is the treatment of choice. High-dose chemotherapy followed by stem cell transplantation is appropriate treatment for suitably selected patients. For patients who are not candidates for stem cell transplantation, lower intensity chemotherapy regimens, including alkylating agent-based regimens and the use of high-dose corticosteroids, can produce clinically important and durable responses.

Investigational Therapies: The role of nonmyeloablative donor transplantation for treatment and the exact role of antiangiogenesis agents are being investigated, as is whether bisphosphonates have an antitumor effect in this disorder. The optimal conditioning regimens for autologous stem cell transplant are also being explored.

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RESOURCES

207, 241, 350

52 Nezelof Syndrome

**Richard A. Insel, MD,
Blake G. Scheer, MD,
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DEFINITION: Nezelof syndrome is associated with severe T-cell immunodeficiency, normal or increased immunoglobulin level, and decreased antibody function. It is considered a form of severe combined immunodeficiency (SCID), although it is not considered a distinct genetic type per se, but may be a clinically less severe form of the disease.

SYNONYMS: Thymic dysplasia with normal immunoglobulins; Cellular immunodeficiency with abnormal immunoglobulin synthesis; Combined immunodeficiency with predominant T-cell defect.

DIFFERENTIAL DIAGNOSIS: Severe combined immunodeficiency; Acquired immunodeficiency syndrome.

SYMPTOMS AND SIGNS: Patients with Nezelof syndrome have symptoms similar to patients with SCID, but at times these may be milder and may present later in infancy. Recurrent infections occur in infancy or childhood and may be associated with failure to thrive and chronic diarrhea and malabsorption. These may include oral candidiasis that is recalcitrant to therapy, infection with *Pneumocystis carinii*, recurrent bronchopulmonary infections, and bacterial otitis media, severe measles or varicella, or other opportunistic infections.

ETIOLOGY/EPIDEMIOLOGY: The genetic abnormality is unknown but the disorder arises as a variant form of SCID. Deficiency of the enzyme adenosine deaminase,

which causes SCID, is responsible for some cases. The disorder may show an autosomal-recessive inheritance. Affected siblings in a kinship may show variation in the degree of T-cell and B-cell immunodeficiency.

DIAGNOSIS: The diagnosis should be suspected based on decreased CD3 total and CD4 helper T-lymphocytes, decreased T-cell function, and normal to increased immunoglobulin levels. Some immunoglobulin classes such as IgM may be at a normal level, with others such as IgG marginally decreased. At times, increased IgE levels are observed. Antibody responses to immunization are decreased. Lymphopenia may be present.

TREATMENT

Standard Therapies: Treatment is bone marrow transplantation from a histocompatible HLA-identical sibling. If such a donor is not available, transplantation should be performed with a T-cell depleted marrow from a haploidentical half-matched family member or an HLA-matched unrelated donor.

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RESOURCES

193, 218, 359

53 Islet Cell Tumors of the Pancreas

Terry C. Lairmore, MD

DEFINITION: Islet cell tumors are derived from neuroendocrine cells that populate the endocrine pancreas during embryologic development. Neuroendocrine tumor (NET) is a more appropriate term that encompasses neoplasms of the pancreatic islet cells, carcinoid tumors, and neoplasms arising in the dispersed system of APUD cells.

SYNONYMS: Pancreatic islet cell tumors; Neuroendocrine tumors of the pancreas.

DIFFERENTIAL DIAGNOSIS: Reactive hypoglycemia; Factitious hypoglycemia; Renal failure.

SYMPTOMS AND SIGNS: The symptoms and signs of NET of the pancreas and gastrointestinal (GI) tract result

from the specific hormone product secreted or the local effect of the tumor mass. The following symptoms and signs are categorized according to the specific hormone over-secreted: *insulinoma*, confusion and bizarre behavior associated with fasting, need for frequent sugar intake, weight gain; *gastrinoma* (Zollinger-Ellison syndrome [see also under Endocrine Disorders]), reflux esophagitis, secretory diarrhea, abdominal pain; *pancreatic polypeptide*, no known symptoms or signs; *vasoactive-intestinal peptide*, secretory diarrhea, hypokalemia, achlorhydria; and *glucagonoma*, hyperglycemia, migratory erythematous rash, and hypoaminoacidemia.

ETIOLOGY/EPIDEMIOLOGY: Islet cell tumors of the pancreas occur with an estimated frequency of 1–2 per million population. Sporadic insulinomas and gastrinomas have no known sex or ethnic predilection. Neuroendocrine tumors of the pancreas and GI tract also occur in association with several hereditary endocrine cancer syndromes. These include multiple endocrine neoplasia type 1 and von Hippel-Lindau syndrome.

DIAGNOSIS: In general, radiographic tests are not indicated until the biochemical diagnosis is established. Zollinger-Ellison syndrome is diagnosed by the finding of an inappropriately elevated fasting serum gastrin level in association with gastric acid hypersecretion. The diagnosis is confirmed by an abnormal secretin stimulation test. Insulinoma is best diagnosed during a supervised fast with the measurement of plasma levels of glucose, insulin, and C-peptide at frequent intervals. Sulfonylureas should also be measured to exclude the surreptitious administration of

oral hypoglycemic drugs, and antiinsulin antibodies should be measured to exclude exogenous insulin administration.

TREATMENT

Standard Therapies: Functional neuroendocrine tumors or those that carry a significant risk of malignancy should be surgically removed. This consists of complete exposure of the pancreas, intraoperative ultrasonography, and inspection and palpation of the gland by an experienced endocrine surgeon. Small, circumscribed, likely benign tumors are enucleated. Major pancreatic resection (distal pancreatectomy, pancreaticoduodenectomy) is appropriate for large, multiple, or malignant tumors.

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RESOURCES

30, 82, 354

54 Pheochromocytoma

William M. Manger, MD, PhD

DEFINITION: Pheochromocytoma, a neuroendocrine tumor, secretes catecholamines (mainly epinephrine and norepinephrine, rarely dopamine) that cause sustained and/or paroxysmal hypertension and a large variety of manifestations. Of these tumors, 98% occur in the abdomen (90% in the adrenal medulla) or pelvis, <2% in the chest, and <0.1% on the neck or base of the skull. About 20% are familial, usually occur in the adrenal medulla, and are often bilateral. About 10% are malignant, but these cannot be differentiated from benign tumors except by evidence of metastatic or invasive lesions.

SYNONYM: Paraganglioma, when occurring in extra-adrenal sites.

DIFFERENTIAL DIAGNOSIS: Neurogenic hypertension (the most common); All hypertension of uncertain cause; Anxiety; Panic attacks; Hyperthyroidism; Paroxysmal tachycardia; Hyperdynamic β -adrenergic circulatory state; Menopause; Vascular headache; Coronary insufficiency syndrome; Acute hypertensive encephalopathy; Intracranial lesions; Autonomic hyperreflexia; Diencephalic seizure; Toxemia of pregnancy (or eclampsia with convulsions); Carcinoid; Familial dysautonomia; Acrodynia; Neuroblastoma; Ganglioneuroblastoma; Ganglioneuroma;

Adrenal medullary hyperplasia; Clonidine withdrawal; Baroreflex failure; Factitious (induced by certain drugs); Hypoglycemia; Reaction to monoamine oxidase inhibitors; Fatal familial insomnia.

SYMPTOMS AND SIGNS: Symptoms and signs result mainly from hemodynamic and metabolic effects of excess circulating catecholamines; numerous peptides may be secreted by these tumors and cause clinical manifestations. Most frequent symptoms are severe headache and inappropriate generalized sweating and palpitations (with or without tachycardia). Other manifestations include anxiety, tremulousness, nausea, vomiting, chest and abdominal pain, weight loss, constipation, diarrhea, paresthesias, pallor, rarely flushing, hypertensive retinopathy, and fever. Paroxysmal attacks usually occur one or more times weekly and last less than 15 minutes. Arrhythmias are frequent, and occasionally catecholamine cardiomyopathy occurs. Approximately 50% of affected persons have sustained hypertension; others have paroxysmal hypertension, and a few remain normotensive. Familial pheochromocytoma may be associated with multiple endocrine neoplasia (MEN), von Hippel-Lindau disease (VHL), carotid body or multiple paragangliomas, and neurofibromatosis type-1. Coexistence of pheochromocytoma with medullary thyroid carcinoma (MTC) or C-cell hyperplasia and sometimes with parathyroid neoplasms and hyperplasia constitutes MEN type-2a. Coexistence of pheochromocytoma with MTC, mucosal neuromas, thickened corneal nerves, alimentary tract ganglioneuromatosis, and sometimes a marfanoid habitus constitutes MEN type-2b. Hyperparathyroidism occurs in about 50% of patients with type 2-a, but rarely in type-2b. Pheochromocytomas coexist in about 14% of patients with VHL disease, which is characterized by hemangioblastoma of the central nervous system and retinal angioma. Renal and pancreatic cysts, renal carcinoma, and cystadenoma of the epididymis may coexist.

ETIOLOGY/EPIDEMIOLOGY: The etiology is unknown. There is no sex predilection in adults, but before puberty it is more common in boys. Tumors may occur at any age, with the highest frequency in the fourth and fifth decades. About 20% of pheochromocytomas are familial with an autosomal dominant inheritance and are due to genetic mutations: *RET* protooncogene on chromosome 10 for MEN type-2a and 2b syndromes, on chromosome 3p for VHL, on chromosome 11q for carotid body and multiple paragangliomas, and on chromosome 17q for neurofibromatosis. Familial tumors are usually bilateral but also may be multicentric.

DIAGNOSIS: The diagnosis must be made or excluded definitively, because if unrecognized, pheochromocytoma will nearly always result in the patient's death. Measurement of plasma catecholamines or 24-hour urinary total metanephrines is favored for screening patients, because they detect pheochromocytoma in more than 95% of cases, and invariably detect those with sustained hypertension due to circulating catecholamines. Drugs that interfere with tests (e.g., labetalol, catecholamines, L-dopa, tricyclic antidepressants, phenoxybenzamine, busparone, and some vasodilators) must be avoided. Differentiation between neurogenic hypertension and pheochromocytoma with mildly elevated plasma catecholamines may be made with the clonidine suppression test, which decreases catecholamines to normal levels if elevations are not due to pheochromocytoma. When diagnosis has been established biochemically, tumor localization is required. Usually, this can be done by CT scan or MRI.

TREATMENT

Standard Therapies: Ninety percent of pheochromocytomas are successfully removed by surgery. Preoperative α - and β -adrenergic blockade may be needed to control hypertension and arrhythmias, respectively. Many tumors can be removed by laparoscopy. Multiple or large (>8cm) tumors may require a transperitoneal approach, or special surgery may be needed if the tumor is in the chest, neck, or base of skull. With familial disease, coexisting thyroid and parathyroid lesions are treated after pheochromocytoma excision. Chemotherapy and radiotherapy may be helpful in managing malignant pheochromocytomas; adrenergic blockers and metyrosine may control manifestations of hypercatecholemlia.

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RESOURCES

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55 Polycythemia Vera

**Kenneth M. Algazy, MD,
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DEFINITION: Polycythemia vera (PV) is a clonal neoplastic disorder characterized by an increased production and circulating numbers of all three blood elements, RBCs, white blood cells and platelets. Patients may develop symptoms of hyperviscosity and thrombotic complications, secondary to their very high red blood cell (RBC) count and marked thrombocytosis. After a few to 20 or more years, the disease “burns out,” the bone marrow becomes fibrotic, and the patient’s picture may mimic that of myelofibrosis, with splenomegaly, extramedullary hematopoiesis, and transfusion dependency.

SYNONYMS: Polycythemia vera; Polycythemia rubra vera.

DIFFERENTIAL DIAGNOSIS: One must distinguish PV from secondary polycythemia, or more accurately secondary erythrocytosis, a physiologic reaction rather than a neoplastic reaction. In secondary erythrocytosis, the RBC number and mass are increased either as a response to hypoxia or due to aberrant production of or enhanced response to erythropoietin. Generally the white blood cells and platelets are present in normal numbers; often underlying pulmonary or cardiac disease is evident, or a tumor (renal, cerebral) secreting erythropoietin is discovered. Rare familial forms of secondary erythrocytosis can be attributed to increased sensitivity to erythropoietin or to abnormal high-oxygen affinity variants of hemoglobin. High-altitude erythrocytosis should be considered if the patient has been living at above 3,000 meters. So-called “stress polycythemia” is due to a contracted blood volume (with a total normal number of circulating RBCs).

SYMPTOMS AND SIGNS: This disorder is usually insidious in onset, generally appearing first in the sixth or seventh decade of life. It may be discovered serendipitously on routine testing, or the patient may complain of headache, weakness, pruritis, dizziness, or sweating; or a thrombotic event may be the presenting symptom. About one third of patients develop thrombotic complications, notably cerebrovascular accident, myocardial infarction or angina, and spontaneous deep vein thrombosis or pulmonary embolus; even mesenteric artery thrombosis and Budd-Chiari syn-

drome (hepatic vein thrombosis) have been noted in some series of patients. From the rapid turnover of blood-forming elements in the marrow, high serum uric acid levels and complicating gout have been observed. Severe pruritis can be aggravated by a hot shower, and may be secondary to the release of histamine from increased numbers of mast cells in the skin. Easy bruising or gum bleeding has also been frequently observed in these patients.

ETIOLOGY/EPIDEMIOLOGY: PV is caused by a malignant transformation of a single progenitor cell that proliferates in the bone marrow, at a variable rate, eventually to become the predominant hematopoietic precursor cell. At diagnosis, about one fourth of patients have an abnormal karyotype, and this percentage increases as the disease progresses, but there does not seem to be a strong familial predisposition. The incidence may be slightly higher among Ashkenazic Jews of Northern European ancestry than in the general population, where the incidence has varied from 5 to 20 per million people.

DIAGNOSIS: The diagnosis of PV should be suspected whenever a patient presents for care with any of the above signs or symptoms and a hematocrit above 50%. The classic presentation of full-blown disease is one of erythrocytosis, leukocytosis, thrombocytosis and splenomegaly; early on, patients may have only some of these findings. All three blood cell lines are increased in number; absolute neutrophilia is very common. Occasional neutrophil precursors (metamyelocytes, myelocytes) are present in the peripheral blood. Increased numbers of basophils are commonly seen. Blood levels of vitamin B₁₂ and uric acid are usually increased above normal. Platelet counts commonly are above 600,000/mm³ and above 1,000,000/mm³ in 10% of patients. Arterial partial pressure of oxygen (PaO₂) is decreased, as low as 65 torr, with normal or near normal oxygen saturation values. Splenomegaly develops later in the course of the disease when extramedullary hematopoiesis occurs, due to myelofibrosis. In secondary erythrocytosis, only the red cell number is increased; the neutrophil and platelet counts are generally normal, unless underlying infection is present (e.g., in chronic lung disease). Measurement of total red cell mass, while diagnostically useful, is difficult and expensive.

TREATMENT

Standard Therapies: There are two stages of PV requiring different treatment approaches. In the first, or “plethoric”

phase, problems relate to the increased circulating red cell mass: thromboses (cerebrovascular, cardiac, mesenteric), possible hyperviscosity (headache), and bleeding (mucous membrane). The therapeutic goal is to reduce the hematocrit, by repeated phlebotomy. About 500 mL of whole blood (less for patients weighing <50 kg, or with cardiac disease) are removed by venesection every 2–4 days to maintain the hematocrit at <50%. This is repeated periodically until iron-deficiency anemia develops, limiting the autonomous generative capability of the marrow. Once iron deficiency develops, the patient's hematocrit and hyperviscosity can be controlled. Phlebotomy alone will effectively control the hematocrit level and concomitant symptoms but not leukocytosis, thrombocytosis, pruritis, or hyperuricemia (and gout). Additional treatments in the "plethora phase" suppress the bone marrow production of all cellular elements: when bleeding or thrombotic complications have occurred or are threatened (platelet count over 800,000/mm³), myelosuppression is given in the form of hydroxyurea, busulfan, chlorambucil, or radioactive phosphorus (³²P). Hydroxyurea is easy to administer, short acting, and therefore safe for long-term suppressive therapy. Busulfan, chlorambucil, and ³²P are also effective for long-term control, but appear to carry a greater risk of inducing a leukemic transformation of PV. Anagrelide is useful for prevention of thrombotic complications from

extreme and uncontrolled thrombocytosis. Pruritis is not generally affected by phlebotomy or myelosuppression until remission is induced; antihistamines are not effective, but UV light treatments with psoralens and interferon- α may help some patients. In the "spent phase" of PV, the marrow is "burned out" and the spleen markedly enlarges to make blood cells. The treatment of PV at this stage is symptomatic. Paradoxically, repeated blood transfusions may be required to support the RBC count of the patient. Thrombocytopenia may become severe and symptomatic. Splenectomy should be considered at that point, when transfusion requirements become great, or if the enlarged spleen becomes very uncomfortable to the patient. In 1986 the Polycythemia Vera Study Group reported that the median survival from diagnosis was 13.9 years for patients receiving phlebotomy alone, and 11.8 years for those treated with ³²P. Causes of death were attributed to thrombotic complications in 31%, and leukemia eventually developed in 19%.

Investigational Therapies: Interferon could be considered for cases difficult to control by other means. Bone marrow transplantation has been used with success on a few occasions. It should only be considered for end-stage, "burned out" cases, extremely difficult to manage in other ways.

56 Pseudomyxoma Peritonei

Paul H. Sugarbaker, MD

DEFINITION: Pseudomyxoma peritonei is characterized by the accumulation of mucus and tumors composed of mucus-secreting epithelial cells throughout the peritoneal space.

SYNONYMS: Jelly belly; Mucinous peritoneal carcinomatosis; Perforated appendiceal cystadenoma or cystadenocarcinoma; Appendiceal cancer.

DIFFERENTIAL DIAGNOSIS: Peritoneal mesothelioma; Ovarian cancer; Serous papillary cancer of the peritoneum; Malignant peritoneal effusions from gastric cancer; Colon cancer or small bowel adenocarcinoma; Ascites from any cause.

SYMPTOMS AND SIGNS: A common symptom in a male is mucoid fluid diagnosed at the time of a hernia re-

pair for either an inguinal or umbilical hernia. A common symptom in a female is a cystic ovarian mass, usually on the right, but often bilateral. In both males and females, appendicitis often calls attention to the disease at the time of appendectomy. Another common symptom is gradually expanding abdominal girth. Infertility may also occur. Some patients with no specific symptoms have had a CT scan that shows the characteristic distribution of mucinous fluid and tumor throughout the abdomen and pelvis.

ETIOLOGY/EPIDEMIOLOGY: Most patients have an appendiceal adenoma or mucinous carcinoma that has perforated the appendix and caused a release of the tumor cells into the free peritoneal cavity. Rarely, a mucinous adenocarcinoma of the small bowel, of the large bowel, or of the gallbladder will perforate and become widely distributed on the peritoneal surfaces. The mucinous tumor cells in copious mucoid fluid do not invade the peritoneal surfaces as most cancers would; they distribute themselves in a characteristic fashion throughout the abdominal and pelvic space. They accumulate in areas where the peritoneal

fluid is absorbed. The incidence of the disease is the same in males and females. However, the manifestations of early disease are unique in women. Ovulation causes a sticky ovarian surface with blood clot present at the site of the Graafian follicle. Tumor cells adhere and then progress at this site to cause a multicystic ovary, in which the cysts are filled by mucoid fluid.

DIAGNOSIS: The diagnosis may be obtained through biopsy or by definitive findings on CT scan of the abdomen and pelvis. Minimally invasive procedures are preferred to establish a diagnosis because tumor cell implantation at the site of surgical trauma is a consistent finding. If the diagnosis is made at the time of exploratory surgery, appendectomy should be performed; mucoid fluid should be obtained for histopathologic and cytologic examination, and the abdomen then closed for definitive treatment at a pseudomyxoma peritonei referral center.

TREATMENT

Standard Therapies: The curative approach, which cures approximately 75% of patients, depends on combined treatment strategies. First, a cytoreductive approach is used to remove visible tumor. Step 2 involves intraperitoneal chemotherapy with mitomycin C used at the time of sur-

gery while the abdomen is still open. In the postoperative period, the same series of tubes and drains is used to administer 5 days of intraperitoneal chemotherapy with 5-fluorouracil. If the disease recurs, second-look surgery is indicated. Reoperative surgery, in patients who show a small volume of recurrent disease, has a 75% cure rate.

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RESOURCES

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57 Acquired Pure Red Cell Aplasia

Neal Young, MD

DEFINITION: Acquired pure red cell aplasia (PRCA) is a hematologic disease in which only erythrocyte production is affected. Typical patients have severe, transfusion-dependent anemia with the absence of reticulocytes in the peripheral blood and of erythroid precursor cells in the bone marrow.

DIFFERENTIAL DIAGNOSIS: Diamond-Blackfan anemia (constitutional pure red cell aplasia); Transient erythroblastopenia of childhood; Transient aplastic crisis; Myelodysplasia; Large granular lymphocytic leukemia.

SYMPTOMS AND SIGNS: Patients present with symptoms of anemia. In younger patients, fatigue and lassitude, dyspnea on exertion, and tinnitus are most frequent; new-onset or worsening angina may occur in the older individual. Physical examination shows only pallor. Lym-

phadenopathy and splenomegaly suggest alternative diagnoses.

ETIOLOGY/EPIDEMIOLOGY: Usually, older individuals are affected, but there is no gender preference. A clear viral etiology—chronic B19 parvovirus—accounts for a significant minority of cases. In others, the disease is idiopathic but probably has an immunologic pathophysiology, with T cell-mediated suppression of erythropoiesis. In a third group, PRCA is associated with myelodysplasia, and there may be cytogenetic abnormalities of the bone marrow such as 5q-. Pure red cell aplasia also accompanies chronic lymphocytic leukemia.

DIAGNOSIS: The morphologic diagnosis rests on the typical appearance of the bone marrow with absent erythroid precursors. With parvovirus infection, pathognomonic giant erythroblasts may occur. In myelodysplasia,

other bone marrow abnormalities may be observed, such as hypogranulated myeloid precursor cells or micromegakaryocytes. Chronic parvovirus infection is suggested by evidence of immunodeficiency—congenital, acquired (AIDS), or iatrogenic (immunosuppressive drugs or chemotherapy)—and is diagnosed by the finding of viral DNA in blood, usually in the absence of specific antibodies to B19. Research laboratories can establish the presence of inhibitory lymphocytes.

TREATMENT

Standard Therapies: Administration of commercially available immunoglobulin can ameliorate or cure parvovirus infection by replacing absent neutralizing antibodies to the virus. For immunologically mediated pure red cell aplasia, immunosuppressive agents usually are used in sequence (e.g., a course of corticosteroids followed by cyclosporine, antithymocyte globulin, azathioprine, or cyclophosphamide) until a response is observed. Treatment

of underlying chronic lymphocytic leukemia may also improve PRCA. Most patients can be expected to respond to some form of appropriate therapy; in the minority who prove refractory, blood can be replaced by transfusion, usually two units of packed red cells every 2 weeks. Transfusion should be to levels adequate for normal activity. Chronic transfusions should be accompanied by iron chelation therapy with desferioxamine to avoid secondary hemochromatosis.

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RESOURCES

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58 Henoch-Schönlein Purpura

Frank T. Saulsbury, MD

DEFINITION: Henoch-Schönlein purpura (HSP) is an acute small vessel vasculitis that primarily affects children. The dominant clinical manifestations are purpura, arthritis, abdominal pain, gastrointestinal bleeding, and nephritis. The clinical features are a consequence of widespread leukocytoclastic vasculitis subsequent to IgA deposition in vessel walls.

SYNONYM: Anaphylactoid purpura.

DIFFERENTIAL DIAGNOSIS: Necrotizing vasculitides; IgA nephropathy.

SYMPTOMS AND SIGNS: Cutaneous purpura concentrated on the legs and buttocks is a constant feature. The purpuric lesions may be preceded briefly (generally <24 hours) by urticarial or maculopapular lesions. The characteristic rash consists of crops of palpable purpura 2–10 mm in diameter. Arthritis occurs in approximately 75% of patients, and commonly involves the knees and ankles. The arthritis may be acutely painful and incapacitating, but it is self-limited and nondeforming. Gastrointestinal involvement occurs in 50%–75% of patients. Colicky abdominal pain, vomiting, and bleeding are the dominant features.

Rare gastrointestinal complications include intussusception and massive gastrointestinal bleeding. Nephritis occurs in 40% of patients. The clinical hallmark of HSP nephritis is hematuria. Although microscopic hematuria is a constant feature, 25% of patients with nephritis have gross hematuria. Proteinuria occurs in conjunction with hematuria in two thirds of patients. Nephritis may become chronic. Approximately 30%–50% of patients have persistent microscopic hematuria or proteinuria in long-term follow-up, but only approximately 1% of patients progress to end-stage renal disease. Otherwise, HSP is an acute, self-limited illness that generally lasts 2–4 weeks. One third of patients experience recurrence of symptoms, usually within 4 months of the original episode.

ETIOLOGY/EPIDEMIOLOGY: The etiology of HSP is unknown, but it is clear that IgA1 but not IgA2 plays a pivotal role in the immunopathogenesis of HSP. The reasons for the exclusive involvement of IgA1 are unknown, but defective glycosylation of IgA1 may contribute to this phenomenon. Henoch-Schönlein purpura is the most common acute vasculitis affecting children, with an incidence of approximately 10 cases per 100,000 children per year. The mean age of patients is 6 years; 90% are younger than 10 years. Boys are affected slightly more often. Most patients present in the fall and winter months, and HSP often follows a respiratory infection. Anecdotal reports have im-

plicated a wide variety of pathogens, but no single pathogen has emerged as a dominant etiologic agent. However, preceding or concomitant group A beta hemolytic streptococcal infection is present in a substantial minority of patients.

DIAGNOSIS: Diagnosis is based on the presence of typical clinical manifestations. Serum IgA concentrations are increased in 50% of patients, but there is no diagnostic laboratory test for HSP. Laboratory studies are useful only to exclude other conditions that resemble HSP.

TREATMENT

Standard Therapies: Corticosteroids are effective in treating arthritis and abdominal pain, but no evidence exists that they have any effect on the purpura, duration of the illness, or frequency of recurrences. Patients with severe nephritis should receive high-dose intravenous methylpred-

nisolone followed by oral corticosteroids plus an immunosuppressive agent, either azathioprine or cyclophosphamide.

Investigational Therapies: Dapsone, plasmapheresis, and factor XIII infusions are being studied in patients with prolonged or severe HSP.

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RESOURCES

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59 Idiopathic Thrombocytopenic Purpura

Kenneth M. Algazy, MD

DEFINITION: Idiopathic thrombocytopenic purpura is an autoimmune destruction of platelets producing thrombocytopenia.

SYNONYMS: Autoimmune thrombocytopenic purpura; Acute thrombocytopenic purpura; Chronic idiopathic thrombocytopenic purpura.

DIFFERENTIAL DIAGNOSIS: Thrombotic thrombocytopenic purpura; Anticardiolipin syndrome; Thrombocytopenia associated with other hematologic disorders; Drug-induced thrombocytopenia; Heparin-induced thrombocytopenia; Henoch-Schönlein purpura; Other vascular purpuras.

SYMPTOMS AND SIGNS: The disease can be seen in an acute state in children. This state appears to follow a viral infection and is generally self-limiting. The platelet count will return to normal even when no therapeutic intervention is attempted. In the adult form, it can occur either by itself or as part of a collagen vascular disease such as systemic lupus erythematosus. In both children and adults, the disease presents as petechiae, purpura, or bleeding from mucous membranes such as the oral or nasal epithelium. Petechiae and purpura are most prominent in the lower extremities.

ETIOLOGY/EPIDEMIOLOGY: The disorder is caused by antibodies directed against various portions of the platelet. The antibodies can be the result of induction by an acute viral illness or by a collagen vascular process. This condition can be seen as an initial or later symptom of HIV disease.

DIAGNOSIS: The diagnosis is based on the presence of thrombocytopenia with generally normal hemoglobin and white count with no evidence of recent new drug use and possibly after an innocuous upper respiratory tract infection. The platelet count can be reduced to any value lower than normal or lower than the patient's baseline value. An HIV test should be done in all patients presenting with thrombocytopenia to rule out an associated HIV infection.

TREATMENT

Standard Therapies: Standard therapy, in the pediatric and adult age range, involves the use of steroids. Prednisone can be used. In children, frequently the thrombocytopenia is simply observed. Either initially or shortly after steroids have been given, if the platelet response is not adequate, intravenous immunoglobulins can be administered. If the patient continues to require higher doses of steroids than deemed advisable or if immunoglobulins have to be continuously repeated, splenectomy can be effective in inducing remissions. In patients who are Rh(D)-positive, anti-D can be administered, which is much less expensive than intravenous immunoglobulins and almost as effective. Additionally, if anti-D is repeated for several months,

the disease may go into spontaneous remission, whereas with immunoglobulin therapy, sustained remissions are infrequent.

Investigational Therapies: Various therapeutic interventions have been suggested. Immunosuppressive agents such as cyclophosphamide, azathioprine, 6-mercaptopurine, vincristine, danazol, interferon, and cyclosporine have been considered. In addition, abnormal B-cell production of immunoglobulins can be challenged by adding rituximab. Colchicine has also been found to be effective by some and, in addition, in unusual circumstances, platelets can be loaded with chemotherapeutic agents such as vin-

blastine to produce destruction of reticuloendothelial cells that are responsible for platelet destruction.

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RESOURCES

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60 Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome of Adults

Kenneth M. Algazy, MD

DEFINITION: Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome of adults are characterized by a reduction in the platelet count due to consumption related to widespread thromboses.

SYNONYM: Moschcowitz disease.

DIFFERENTIAL DIAGNOSIS: Idiopathic thrombocytopenic purpura; Heparin-induced thrombocytopenia; Vasculitis.

SYMPTOMS AND SIGNS: The disease is characterized by a classic pentad of features. These include microangiopathic hemolytic anemia, thrombocytopenic purpura, neurologic symptoms, renal disease, and fever. Thrombotic thrombocytopenic purpura usually occurs in previously healthy individuals, but the syndrome is also associated with other disorders. It can be found in association with infections, some of the newer antiplatelet agents, cancer, collagen vascular diseases, pregnancy, and HIV disease. The disorder can also be seen in non-Hodgkin lymphoma.

ETIOLOGY/EPIDEMIOLOGY: These disorders appear to be due to either an inhibitor of von Willebrand factor–cleaving protease or the constitutional deficiency of this protease.

DIAGNOSIS: The diagnosis is suggested by thrombocytopenia in the presence of the aforementioned clinical situ-

ations. The characteristic morphologic picture is of fragmentation of red cells seen on the peripheral blood smear. The presence of fragmented red cells in association with symptoms and signs, particularly the pentad mentioned previously, secure the diagnosis.

TREATMENT

Standard Therapies: Plasma infusion and exchange effectively decreases the presence of an inhibitor and replaces the inhibited or absent protease, and therefore can be curative. In refractory patients, the many manipulations that have been used to treat the disorder include splenectomy, steroids, immunosuppression, vincristine, immunoabsorption, and intravenous immunoglobulins.

Investigational Therapies: Eventually, the protease will be efficiently prepared, and rather than exchanging plasma, administration of the protease may treat the disease.

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RESOURCE

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61 Shwachman-Diamond Syndrome

Susan F. Burroughs, MD

DEFINITION: Shwachman-Diamond syndrome (SDS) is an inherited disorder characterized by absolute requirements of pancreatic acinar and bone marrow dysfunction. Patients may have pancreatic insufficiency with malabsorption and intermittent or persistent cytopenias, most commonly neutropenia. Other supportive features include short stature, skeletal changes, and liver abnormalities.

SYNONYMS: Shwachman syndrome; Shwachman-Bodian syndrome; Shwachman-Diamond-Oski syndrome; Lipomatosis of pancreas, congenital; Pancreatic insufficiency and bone marrow dysfunction.

DIFFERENTIAL DIAGNOSIS: Cystic fibrosis; Pearson marrow-pancreas syndrome; Congenital neutropenia (Kostmann's syndrome); Johanson-Blizzard syndrome; Metaphyseal chondroplasia (McKusick type).

SYMPTOMS AND SIGNS: Individuals with SDS typically have one to several of the following: signs and symptoms of fat malabsorption, short stature, delayed puberty, skeletal changes including rib cage abnormalities and metaphyseal dysostosis, pallor, fatigue, bleeding, and frequent infections. Less frequently, they may have psychomotor delay, hypotonia, liver, skin, and dental abnormalities, endocardial fibrosis, renal tubular acidosis and diabetes mellitus. Symptoms of fat malabsorption may improve with age, because some patients have improvement in pancreatic function. Pancytopenia may develop due to bone marrow failure with aplastic anemia or myelodysplastic syndrome, and it may evolve into acute myeloid leukemia.

ETIOLOGY/EPIDEMIOLOGY: The cause of this syndrome is unknown, although it is a congenital disorder with what appears to be autosomal-recessive inheritance, affecting males and females in a ratio of approximately 1.7:1. The location and nature of the genetic defect are the subject of intensive research efforts, and the gene has been mapped to a centromeric region of chromosome 7. Due to the lack of a specific diagnostic test and variability in severity of the syndrome, estimates of the incidence of this disorder have ranged from 1 in every 20,000 to 1 in every 200,000 births.

DIAGNOSIS: The diagnosis of pancreatic acinar dysfunction may be made by the pancreatic stimulation test or by indirect indicators of pancreatic acinar dysfunction (72-hour fecal fat and/or serum trypsinogen). A sweat test can rule out cystic fibrosis. Imaging tests of the pancreas (CT, MRI, or ultrasonography) can be used to document fatty infiltration or

atrophy of the pancreas. Documentation of cytopenias should show persistent or intermittent abnormalities, including an absolute neutrophil count less than 1,500/mm³ and/or hemoglobin, hematocrit, or platelet count less than the age-related normal range. A bone marrow biopsy and aspirate with cytogenetics may be used to document cellularity, dysplastic changes, and the presence of any clonal abnormalities such as monosomy 7 or 7q-. Radiography may be used to document skeletal abnormalities.

TREATMENT

Standard Therapies: Pancreatic enzyme replacement therapy and fat-soluble vitamins (A, D, E, and K) are the main treatment for pancreatic insufficiency. High-calorie and/or high-protein diets, prophylactic antibiotics, and transfusions are sometimes used. Growth factors (e.g., granulocyte colony-stimulating factor) have been used to stimulate neutrophil production. Their use may be best limited to short-term courses, as long-term safety in SDS has not been firmly established. Frequent preventive dental care, special services for developmental delays and genetic counseling may be of benefit.

Investigational Therapies: Chemotherapy and bone marrow or peripheral stem cell transplantation are used for the treatment of bone marrow failure syndromes. Several research projects are evaluating the pancreatic acinar cell defect, bone marrow dysfunction and predilection to malignancy, and the genetic basis of SDS. Others are studying bone marrow aspirates and biopsies with cytochemical and immunohistochemical stains and flow cytometry for early identification and characterization of the myelodysplastic changes in SDS patients.

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62 Hereditary Hemorrhagic Telangiectasia

**Alan E. Guttmacher, MD,
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DEFINITION: Hereditary hemorrhagic telangiectasia (HHT) is a multisystem vascular dysplasia characterized by the presence of multiple arteriovenous malformations (AVMs) that lack intervening capillaries and result in direct connections between arteries and veins.

SYNONYM: Osler-Weber-Rendu (OWR) disease.

DIFFERENTIAL DIAGNOSIS: von Willebrand disease; Ataxia-telangiectasia; CREST syndrome; Hereditary benign telangiectasia; Chronic liver disease.

SYMPTOMS AND SIGNS: Most patients have recurrent epistaxis. Telangiectases of the face, oral cavity, or hands may develop. Telangiectases can occur in the gastrointestinal (GI) tract, most commonly in the stomach and proximal small intestine. Epistaxis and/or GI bleeding can cause mild to severe anemia. Pulmonary AVMs have been reported in 33% of patients and cerebral AVMs in 11%. Spinal AVMs are less common. Hepatic AVMs also occur; although also apparently less common, their frequency is unknown. Any AVM can manifest as hemorrhage. Pulmonary AVMs can lead to transient ischemic attacks, embolic stroke, or cerebral abscess. Migraine headache, polycythemia, and hypoxemia with cyanosis and clubbing of the nails also may be complications. Hepatic AVMs can cause high-output heart failure or portal hypertension. Cerebral AVMs may cause seizure or cerebral hemorrhage.

ETIOLOGY/EPIDEMIOLOGY: This is an autosomal-dominant disorder. Hereditary hemorrhagic telangiectasia type 1 is caused by a mutation in the endoglin gene; HHT type 2 is caused by a mutation in the activin receptor gene *ALK1*. The ethnic and geographic distribution is wide; the incidence in North America is approximately 1 in 10,000.

DIAGNOSIS: The diagnosis is considered definite when three or more of the following criteria are present, and possible or suspected when two of the criteria are present: recurrent spontaneous epistaxis; multiple telangiectases at characteristic sites, including face, lips, oral cavity, and fin-

gers; one or more visceral AVMs (pulmonary, cerebral, hepatic, spinal) or GI telangiectases (with or without bleeding); and family history of HHT. Only limited laboratory genetic testing is available.

TREATMENT

Standard Therapies: Management includes treatment of identified complications such as nosebleeds, GI bleeding, anemia, and AVMs, as well as surveillance for undiagnosed AVMs. All patients should have a brain MRI with and without gadolinium to screen for cerebral AVM once at any age; and, starting at 10 years of age, some combination of contrast echocardiography, chest CT, or chest radiography and arterial blood gas determination to screen for pulmonary AVM approximately every 5 years. For pulmonary AVMs with feeding vessels that exceed 3 mm, transcatheter embolotherapy with detachable balloons or stainless-steel coils is the treatment of choice. Cerebral AVMs greater than 1 cm in diameter are usually treated, if feasible, using neurovascular surgery, embolotherapy, and/or stereotactic radiosurgery. If nosebleeds are not adequately controlled by humidification and daily application of nasal lubricants by the patient, laser ablation or skin grafting may be the most effective interventions. Endoscopic applications of a heater probe, bicap, or laser are the mainstays of treatment for symptomatic GI bleeding. Treatment for cardiac failure or liver failure secondary to hepatic AVMs is problematic.

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63 Thalassemia Major

John N. Lukens, MD

DEFINITION: Thalassemia major is a severe hemolytic anemia caused by mutations involving the α -globin or the β -globin genes of hemoglobin. Blood transfusions are required for growth and long-term survival.

SYNONYM: Cooley anemia.

DIFFERENTIAL DIAGNOSIS: Pyruvate kinase deficiency; Hereditary spherocytosis; Hereditary pyropoikilocytosis; Sickle cell anemia.

SYMPTOMS AND SIGNS: Because α -globin is a component of both fetal and adult hemoglobins, thalassemia major due to α -globin gene mutations is characterized by anemia from birth. Anemia due to β -thalassemia variants becomes apparent only as Hgb F is replaced by Hgb A during the first several months of life. Once manifest, anemia in both α - and β -thalassemia major is attended by pallor, intermittent jaundice, an expanding abdominal girth (due to splenomegaly), and failure to thrive. In the absence of transfusions, the hemoglobin concentration falls to 3–5 g/dL. By 1 year of age, growth retardation is prominent, the head is large with frontal bossing, and the cheekbones are prominent, tending to obscure the base of the nose and to accentuate prominence of the upper teeth (thalassemic facies). In the untreated patient, death usually occurs by age 5 years. A comprehensive chronic transfusion program facilitates growth and prevents skeletal complications. If measures to limit iron overload are not stringent, however, affected individuals are at risk for death from hepatic fibrosis and myocardial hemosiderosis during the second decade of life.

ETIOLOGY/EPIDEMIOLOGY: Approximately 300 different thalassemia mutations exist. α -Globin gene mutations are seen primarily in individuals of South East Asian and African origins, whereas β -globin gene mutations are seen chiefly in individuals of Mediterranean and Middle Eastern descent. Patients with thalassemia major are homozygous or (more often) doubly heterozygous for mutant genes. Each parent has a single mutant gene (thalassemia minor).

DIAGNOSIS: α -Thalassemia major (also known as Hgb H disease) should be suspected at birth in Asian infants

with severe microcytic, hypochromic anemia. The diagnosis is confirmed by the electrophoretic demonstration of Hgb Bart's (in the neonatal period) or Hgb H (after the first months of life). Because of differences in gene mutations, African Americans are not at risk for α -thalassemia major. β -Thalassemia major also is characterized by severe microcytic, hypochromic anemia. Its onset is delayed until after the first 6 months. Red cell morphologic changes are prominent, with nucleated forms, anisocytosis, poikilocytosis, target cells, and basophilic stippling. The diagnosis is confirmed by hemoglobin electrophoresis. Hgb F is the major hemoglobin (70%–95%), Hgb A is absent or greatly decreased, and Hgb A₂ is normal or increased.

TREATMENT

Standard Therapies: Management should be orchestrated by a center having experience with chronic transfusion therapy. Transfusions are started when the hemoglobin falls below 7 g/dL or when growth deviates from the norm. The hemoglobin is maintained above 10 g/dL with a mean hemoglobin of 12 g/dL. Splenectomy may be required for an increasing transfusion requirement. Iron chelation with daily infusions of deferoxamine is started after the first 10–20 transfusions or when the serum ferritin reaches 1,000 ng/mL. Because of the demands of chronic transfusion therapy and the lethal potential of iron overload, allogeneic stem cell transplantation is indicated for patients with HLA-matched family members. Transplantation should be done before the patient is 16 years of age and is most successful if done before the onset of hepatomegaly, portal fibrosis, and iron overload.

Investigational Therapies: Pharmacologic reactivation of γ -globin synthesis with hydroxyurea appears to have benefited some but not most patients.

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64 Thalassemia Minor

John N. Lukens, MD

DEFINITION: Thalassemia minor is a disorder of hemoglobin synthesis characterized by a mild microcytic, hypochromic anemia.

SYNONYM: Thalassemia trait.

DIFFERENTIAL DIAGNOSIS: Iron deficiency anemia; Anemia of chronic disease.

SYMPTOMS AND SIGNS: Individuals with thalassemia minor have no symptoms attributable to the disorder and no abnormal physical findings. The anemia is insufficient to produce pallor. The disorder is suspected because of an abnormal hemogram or detected through family studies done to characterize symptomatic anemia in a relative.

ETIOLOGY/EPIDEMIOLOGY: Thalassemia minor is the most common genetic disorder worldwide. It is due to mutations involving the α -globin or β -globin genes of hemoglobin. α -Globin gene mutations occur primarily in individuals of Southeast Asian or African origins, whereas β -globin mutations had their origins in the Mediterranean basin. Because of global migrations and ethnic intermarriage, however, most individuals with thalassemia minor in North America are unaware of ancestral roots in areas of the world having high prevalence rates of thalassemia.

DIAGNOSIS: Anemia is mild or absent. The red blood cell (RBC) count is elevated, the mean corpuscular volume (MCV) and the mean corpuscular hemoglobin (MCH) are low (mean values 65 fL and 20 pg, respectively), and the mean corpuscular hemoglobin concentration (MCHC) is

normal or only slightly decreased (mean value 31 g/dL RBC). RBC morphology is characterized by target cells and basophilic stippling. Iron deficiency also is associated with low values for MCV, MCH, and MCHC. The two disorders can be differentiated by considering the RBC indices in the context of anemia. Differences in hemogram profiles have made it possible to develop several discriminative functions to distinguish between the two disorders. In the simplest of these, the MCV is divided by the RBC count. A value less than 13 is indicative of thalassemia minor, whereas a value greater than 13 is in keeping with iron deficiency. The diagnosis of α -thalassemia minor can be confirmed by the electrophoretic demonstration of an increase in hemoglobin A₂ (3.4%–8%). There is no readily available test for β -thalassemia minor. This disorder is suspected in the presence of erythrocytosis and a modest decrease in MCV and MCH in the absence of iron deficiency or an abnormal hemoglobin electrophoretic pattern.

TREATMENT

Standard Therapies: No treatment is necessary or indicated. Therapeutic iron should be avoided unless iron deficiency is documented biochemically, as iron absorption is increased. Although rare, iron overload due to long-term iron administration has been described.

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65 Idiopathic Thrombocytosis

Kenneth M. Algazy, MD

DEFINITION: Idiopathic thrombocytosis is characterized by elevation of platelet counts primarily but also potential elevation of white cells in the setting of a myeloproliferative disorder. Although the elevated platelets are the

hallmark of the condition, the disorder frequently involves other cell lines. This is a clonal myeloproliferative disorder that can progress to an acute leukemia.

SYNONYMS: Essential thrombocytosis; Essential thrombocythemia.

DIFFERENTIAL DIAGNOSIS: Secondary thrombocytosis in the postsplenectomy state; Active collagen vascular disease; Other myeloproliferative disorders such as polycythemia vera and chronic myelogenous leukemia.

SYMPTOMS AND SIGNS: The presentation is clinically heterogeneous. Two thirds of patients with essential primary thrombocytosis are asymptomatic. One third present with complications that include thrombosis and/or bleeding in the cerebral, myocardial, and peripheral arterial circulation as well as deep vein thrombosis and pulmonary emboli. The bleeding can be manifested by gastrointestinal, skin, and mucous membrane hemorrhaging. Platelet counts are elevated above normal. The spleen may be enlarged and the patient frequently has iron deficiency anemia due to chronic gastrointestinal bleeding.

ETIOLOGY/EPIDEMIOLOGY: The disorder is caused by a clonal proliferation of bone marrow stem cells that are closest to the platelet. These megakaryocyte-related stem cells appear to be autonomous and may be associated with clonal abnormalities that also involve the erythroid and myeloid line.

DIAGNOSIS: The diagnosis is made by finding an elevated platelet count with hemorrhagic and thrombotic complications or simply found on a routine complete blood cell count. To secure the diagnosis, other causes of thrombocytosis should be ruled out such as rheumatoid arthritis; malignancies of the stomach, ovary, and lung; chronic myelogenous leukemia; and polycythemia rubra vera. In addition, iron deficiency anemia alone, without idiopathic thrombocytosis, can have an elevated platelet

count and under these circumstances the diagnosis may not be apparent until iron has been replenished.

TREATMENT

Standard Therapies: The standard therapy is hydroxyurea, which is frequently sufficient to control the disease for extended periods in most patients. When this fails, anagrelide can be administered. This agent will control the platelet count but has side effects of fluid retention as well as not lasting for a prolonged period so that administration must occur on a regular basis, two to three times daily. Interferon- α has proven to be valuable but produces flulike side effects for the initial weeks of administration. Antiplatelet agents are controversial because some patients affected with this disorder have more of a problem with bleeding than they do with thromboses. An older form of therapy is the use of either busulfan or radiophosphorus. Both of these treatments should be reserved for the very elderly because receiving these drugs for any prolonged period of time can be associated with an increased incidence of leukemic conversion.

Investigational Therapies: Tyrosine kinase inhibitors, similar to those used in chronic myelogenous leukemia, may be used in the future.

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66 Twin-Twin Transfusion Syndrome

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DEFINITION: Twin-twin transfusion syndrome (TTTS), a condition that occurs in approximately 10% of monochorionic twins, is believed to result from uneven exchange of blood between two fetuses through a common placenta.

SYNONYMS: Fetofetal transfusion; Chorioangiopagus twins.

DIFFERENTIAL DIAGNOSIS: Selective growth retardation of a monochorionic twin; Premature rupture of mem-

branes of twin A; Anhydramnios from renal anomaly in one twin.

SYMPTOMS AND SIGNS: While pregnant, the mother may experience rapid increase of abdominal girth, back pain, vaginal spotting, overt signs of preterm labor, premature rupture of membranes, or miscarriage. A woman may also be asymptomatic and diagnosed only during a routine ultrasonographic examination.

ETIOLOGY/EPIDEMIOLOGY: Vascular communications are present in virtually 100% of monochorionic placentas. If the direction or number of communications is

greater from one twin to the other, a net flow of blood occurs from one twin (donor) to the other twin (recipient), causing TTTS. Evenly developed vascular communications may also produce TTTS if unrelated hemodynamic decompensation of one fetus, as in congenital heart disease, occurs. The increased blood flow to the recipient twin results in polyuria and polyhydramnios. Decreased cardiac contractility, tricuspid valve regurgitation, reverse flow in the ductus venosus, pulsatile venous flow (PUVF), hydrops, and fetal death may ensue. The decreased blood flow to the donor twin results in anuria, oligohydramnios, and entrapment within its sac (stuck twin). Absent or reverse end-diastolic velocity in the umbilical artery, PUVF, and death may also occur.

DIAGNOSIS: The diagnosis of TTTS is made by ultrasonography as follows: polyhydramnios in the recipient twin (maximum vertical pocket >8 cm) and simultaneous oligohydramnios in the donor twin (maximum vertical pocket <2 cm) in a sonographically established monochorionic twin gestation.

TREATMENT

Standard Therapies: Serial amniocenteses is used to relieve the polyhydramnios. Data suggest that this may be effective in early stages of the disease, but less so in more advanced cases. Another therapy is occlusion of the placental vascular communications by means of endoscopic fetal

surgery, which stops any further blood exchange between the fetuses, halting the disease. Outcomes appear to be independent of disease severity. Umbilical cord occlusion by means of endoscopic surgery or by ultrasonography to interrupt blood exchange between the twins may also be used, but because this results in the death of one of the fetuses, it is used only in the most advanced stages of the disease.

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67 Wegener Granulomatosis

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DEFINITION: Wegener granulomatosis (WG) is a multi-organ system inflammatory illness associated with granulomatous inflammation and vasculitis.

SYNONYMS: Wegener disease; Pathergic granulomatosis.

DIFFERENTIAL DIAGNOSIS: Polyarteritis nodosa; Microscopic polyangiitis; Churg-Strauss syndrome; Henoch-Schönlein purpura; Systemic lupus erythematosus; Lymphoma; Lymphomatoid granulomatosis; Mycobacterial and deep fungal infections; Sarcoidosis; Goodpasture syndrome.

SYMPTOMS AND SIGNS: Symptoms include fatigue, fever, and weight loss. Scleritis, orbital pseudotumor with proptosis, conjunctivitis, and dacrocystitis may occur. Serous otitis media with conductive hearing loss and granulomatous inflammation in the middle ear, as well as nasal bleeding and crusting, nasal septal perforation, and

“saddle-nose” deformity may occur. Other symptoms include pan-sinusitis with bony erosions and subglottic stenosis. In the lungs, there may be pulmonary nodules and cavities (Insert Figs. 45 and 46), alveolar hemorrhage caused by pulmonary capillaritis, nonspecific infiltrates, bronchiolitis obliterans with organizing pneumonia, and, rarely, bronchocentric lesions leading to bronchial stenosis. There may be mesenteric vasculitis with gastrointestinal hemorrhage, as well as migratory arthritis, often involving the large joints of the lower extremities. Skin may show a palpable purpura, cutaneous ulcerations, and nodules over the elbows that may mimic rheumatoid nodules. Vasculitic neuropathy of the peripheral nerves may be present. Meningeal involvement by granulomatous inflammation, leading to a chronic meningitis presentation, can also occur.

ETIOLOGY/EPIDEMIOLOGY: The cause of WG is unknown. In Western countries, most cases occur in whites, and the disease is believed to be less common among

blacks; however, the disease is known to occur in all races. Typically, patients with WG are middle-aged, but the disease also occurs in the elderly and (rarely) in children. The gender distribution is approximately equal, with perhaps a slight male predominance.

DIAGNOSIS: Because of the numerous mimickers of WG among infectious, malignant, and other types of disorders, confirmation of the diagnosis by biopsy of an involved tissue is critical. Lung biopsies are most likely to yield all three typical histopathologic features (granulomatous inflammation, necrosis, and vasculitis), and pulmonary lesions are often amenable to biopsy through thoracoscopic procedures, which have less morbidity than open-lung biopsies. Kidney biopsies that show segmental, necrotizing glomerulonephritis (often with crescents) may also be diagnostic of WG in the setting of other findings, e.g., clinical or radiologic evidence of nasal, sinus, or lung involvement, or serologic evidence of antineutrophil cytoplasmic antibodies. The finding of granulomatous inflammation is unusual in the kidneys in WG, but glomerulonephritis is the renal equivalent of small vessel vasculitis.

TREATMENT

Standard Therapies: Treatment is based on the concepts of “severe” and “limited” disease. Severe WG is any form of organ involvement that poses an immediate threat either to

the patient’s life or to a vital organ; limited WG is any form of the disease that does not pose such a threat. Severe WG requires treatment with a combination of oral daily cyclophosphamide and high doses of corticosteroids. Limited disease may be treated with methotrexate in lieu of cyclophosphamide. In both severe and limited disease, long-term therapy for months to years is typically required. In the case of severe disease, however, attempts should be made to switch cyclophosphamide to either methotrexate or azathioprine after 3–6 months, assuming that the underlying disease appears controlled, to avoid some of the side effects of cyclophosphamide. Steroids should be tapered and discontinued by 6 months, if possible, and all WG patients treated with the combination of steroids and a cytotoxic agent should be treated with prophylaxis against *Pneumocystis carinii* pneumonia.

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RESOURCES

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