further suggests an immune-mediated mechanism for the disease. One hypothesis is that drug or viral antigens presented to the immune system trigger cytotoxic T-cell responses that persist and destroy normal stem cells. Only 1 in 100,000 patients develops severe AA as an idiosyncratic drug reaction. Whether these individuals have a genetically predisposed sensitivity to common exposures (e.g., nonsteroidal anti-inflammatory drugs, sulfonamides, Epstein-Barr virus) is unknown.

Clinical Presentation

The clinical onset of AA can be insidious or abrupt. Patients often complain of symptoms related to their cytopenias: weakness, fatigue, dyspnea, or palpitations resulting from anemia; gingival bleeding, epistaxis, petechiae, or purpura caused by low platelet counts; or recurrent bacterial infections caused by low or nonfunctioning neutrophils. Results of the physical examination are often normal except in patients with congenital AA, who may have various abnormalities.

Diagnosis and Differential Diagnosis

Diagnostic confirmation of AA requires bone marrow biopsy to confirm hypocellularity and to rule out other marrow processes. Normal bone marrow cellularity ranges from 30% to 50% up to age 70 years and is less than 20% after 70 years of age (E-Fig. 45-1A). In contrast, bone marrow cellularity in patients with AA usually ranges from 5% to 15%, with increased fat accumulation and few or no hematopoietic cells (primarily plasma cells and lymphocytes) (see E-Fig. 45-1B).

In AA, hematopoietic progenitor and precursor cells are morphologically normal but number less than 1% of normal levels, and they are markedly dysfunctional, with a decreased ability to form differentiated progenitor cell colonies in vitro. Evidence of increased blasts, dysplastic hematopoietic cells (e.g., pseudo-Pelger-Huët abnormalities, micromegakaryocytes) (E-Fig. 45-2), and clonal cytogenetically abnormal cells in the peripheral blood or marrow are diagnostic of acute leukemia or myelodysplasia but not AA, even in the setting of a hypocellular marrow.

In young patients, a diagnosis of Fanconi's anemia is made by demonstrating enhanced sensitivity of cultured cells to mitomycin or diepoxybutane-induced chromosomal damage. Although patients with AA typically have a low reticulocyte count from low red blood cell production and a paucity of blood cells (E-Fig. 45-3A) and macrocytic red cells (see E-Fig. 45-3B) on the peripheral smear, patients with other primary marrow disorders may exhibit similar findings.

Treatment and Prognosis

Treatment of AA is based on the severity of disease. Patients with mild cytopenias can be monitored expectantly. However, patients with severe AA based on peripheral blood cells counts (i.e., neutrophil count <500/μL, platelet count <20,000/μL, anemia with corrected reticulocyte count <1%, and marrow cellularity of 5% to 10%) have a poor median survival of 2 to 6 months without treatment. Because most of these patients die of overwhelming infections, supportive care with broad-spectrum antibiotics, antifungal agents, and antiviral agents is warranted for those with advanced neutropenia. Red blood cell and platelet transfusions can help patients who are profoundly symptomatic, along with care given to patients eligible for transplantation.

Current therapeutic approaches to AA focus on replacing the defective HSCs by stem cell transplantation or controlling an overactive immune response. All young patients with severe AA and an HLA-compatible bone marrow donor should be considered for allogeneic bone marrow transplantation, which offers the best chance for definitive cure. Although long-term survival is excellent for patients younger than 30 years transplanted from a sibling donor (75% to 90%), morbidity due to the transplant itself and the management of long-term complications are continuing problems. Outcomes for patients older than 40 years or patients without an HLA-matched related donor are poor.

The presumed immune mechanisms for drug-induced aplasia have encouraged immunosuppressive approaches to the treatment of AA in older patients, in patients who are unable to find a compatible HSC donor, and in those who are otherwise ineligible for stem cell transplantation. Treatment with a combination of antithymocyte globulin (ATG) and cyclosporine (a specific T-cell inhibitor) restores marrow function (i.e., independence from red blood cell or platelet transfusions) in 70% to 80% of patients, and responders have a 5-year survival rate of 90%. Side effects of ATG include anaphylaxis and serum sickness as a result of foreign antigens in the antisera, but these adverse effects usually are self-limited.

Patients often relapse, and recurrence of disease may warrant retreatment with ATG, androgens, and newer immunosuppressive agents. Alemtuzumab, a humanized monoclonal antibody directed against the CD52 protein found on lymphocytes and which has efficacy in other autoimmune diseases, has been as effective as rabbit ATG and cyclosporine in relapsed and refractory severe AA. Eltrombopag, an oral TPO mimetic drug that stimulates platelet production by binding to MPL receptors on megakaryocytes, is an exciting agent for the treatment of severe AA patients. Almost one half of patients treated with eltrombopag exhibited clinically significant responses in all three hematopoietic lineages, with normalization of bone marrow cellularity and trilineage hematopoiesis.

Treatment of AA with traditional chemotherapy such as high-dose cyclophosphamide usually has proved too toxic. Because endogenous cytokine production is usually high in patients with AA, the routine use of growth factors such as G-CSF, EPO, or stem cell factor typically is ineffective. However, in patients with refractory disease, long-term administration of combination cytokines may have some effect in sustaining blood cell counts. Patients who survive initial treatment of AA remain at increased risk for the emergence of other primary hematologic disorders, such as myelodysplasia, leukemia, and paroxysmal nocturnal hemoglobinuria (PNH) for unknown reasons.

Paroxysmal Nocturnal Hemoglobinuria

Definition, Epidemiology, and Pathology

PNH is an uncommon disease characterized by intravascular hemolysis, venous thrombosis, and bone marrow failure. The disease arises from expansion of pluripotent HSCs containing a somatic mutation in the phosphatidylinositol glycan complementation class A *(PIGA)* gene. Loss of *PIGA*, which codes for