a membrane lipid moiety (i.e., glycosyl phosphatidylinositol [GPI]), produces abnormal hematopoietic cells deficient in dozens of proteins that are normally attached to the cell surface by the GPI anchor. Disease manifestations of PNH result from lack of the GPI-linked proteins (CD55 and CD59) that usually protect red blood cells and platelets from complement-mediated attack. Loss of CD55 or CD59 leads to increased immune destruction of blood cells.

Blood cells arising from abnormal PNH clones can have complete (type III cells) or partial (type II cells) GPI deficiency. The degree of GPI deficiency is associated with the severity of the clinical symptoms. GPI-deficient cells typically coexist in the marrow with various populations of normal GPI-expressing cells (type I cells). Small numbers of abnormal PNH clones in patients with AA or myelodysplastic syndrome (MDS) suggest significant overlap in the causes of these three diseases. This led to reclassification of PNH as classic PNH disease and PNH in the setting of another specified bone marrow disorder. Suppression of normal hematopoiesis by the host immune system directly or indirectly by a preceding or coexistent disorder appears to provide a marrow environment favoring selective expansion of PNH stem cell clones and their deficient blood cell progeny over normal hematopoiesis.

Clinical Presentation

Patients are typically younger individuals with chronic complaints of abdominal pain, dysphagia, erectile dysfunction, and intense lethargy due to smooth muscle dystonia resulting from depletion of circulating nitric oxide levels by free hemoglobin. Acute exacerbations may occur intermittently or frequently and are difficult to manage.

Diagnosis and Differential Diagnosis

The diagnosis of PNH is made by identification of complete or partial GPI protein deficiency on red cells and granulocytes, which usually is determined by the loss of CD59, CD55, CD16, or CD24 expression in a clonal population. Laboratory tests reveal ongoing, low-grade intravascular hemolysis with increased lactate dehydrogenase levels correlating with severity of hemolysis and symptoms. Cytopenias, particularly anemia, often render patients transfusion dependent with ongoing hemoglobinuria due to the release of free plasma hemoglobin from intracellular compartments. About 15% of PNH patients have spontaneous resolution of disease without long-term sequelae, suggesting that *PIGA* mutations may appear transiently and disappear spontaneously in normal hematopoietic cell populations for unknown reasons.

Treatment

Treatment of PNH ranges from supportive care with transfusions and iron and folic acid supplementation to allogeneic stem cell transplantation in selected patients for curative intent. Documented venous thrombosis is treated with lifelong full anticoagulation.

Eculizumab is a humanized monoclonal antibody that binds with high affinity to the complement protein C5, preventing terminal complement-mediated intravascular hemolysis in PNH patients. Eculizumab therapy decreases hemolysis and hemoglobinuria, reduces requirements for red blood cell transfusions, improves chronic renal failure, and is associated with significant improvement in quality of life and survival for PNH patients. The incidence of life-threatening thrombotic events is decreased by more than 80%, likely contributing to the significant improvement in overall survival. Although this agent is associated with a theoretical increased risk for meningococcal infections due to complement-mediated blockade, the long-term safety and efficacy of sustained eculizumab therapy administered for more than 5 years appear to outweigh the potential risks of prolonged treatment.

Prognosis

Despite advances in treatment and adequate anticoagulation, PNH remains a life-threatening disease. Venous thrombosis involving the cerebral and intra-abdominal veins occurs in about one half of patients and is the cause of death for up to one third, although the cause of the increased thrombotic risk is not entirely understood. Other causes of morbidity and mortality are side effects of progressive AA and a 5% long-term risk for leukemic transformation. Historically, the median survival from diagnosis is 10 to 15 years, with one third of patients dying within 5 years of the diagnosis. Whether long-term eculizumab therapy can change the natural history of disease is unknown and is the goal of an international registry of PNH patients.

Myelodysplastic Syndrome

Definition and Epidemiology

MDS is a heterogeneous group of blood disorders characterized by ineffective and disordered hematopoiesis in one or more of the major myeloid cell lines: erythroid cells, neutrophils and their precursors, and megakaryocytes. Patients have one or more cytopenias despite normal or increased numbers of hematopoietic cells in the bone marrow. Disordered maturation is accompanied by increased intramedullary apoptosis, which contributes to the decreased release of mature cells into the periphery.

Primary MDS is predominantly a disease of elderly persons and occurs in about 1 of 500 patients between the ages of 60 and 75 years. Most cases are idiopathic. Although often considered a preleukemic disease, the overall risk of MDS transformation to acute myeloid leukemia (AML) is only 25% to 30%. However, identification of characteristic gene deletions (5q−) and translocations diagnostic of MDS and AML subtypes (see Chapter 46) underlines the likelihood of similar mechanisms of clonal myeloid stem cell injury in both disorders.

Pathology

Persons with prior exposure to radiation therapy, chemotherapy, and organic chemicals (e.g., benzene) are at increased risk for secondary MDS. This disorder may occur at any age and comprises 10% to 15% of all diagnosed MDS cases. MDS arising months to years after prior chemotherapy (involving any cytotoxic agent but particularly alkylating agents and anthracyclines), ionizing radiation, radiolabeled antibody therapy, or stem cell transplantation for cancer is called *therapy-related MDS*. Because therapy-related MDS typically evolves swiftly to more