Hemolytic Anemias Caused by Disorders of the Erythrocyte Membrane

Inherited Membrane Abnormalities

Hereditary spherocytosis (HS) is caused by heterogeneous congenital abnormalities in proteins of the erythrocyte cytoskeleton (Table 47-7). Most patients with HS have dominantly inherited mutations in spectrin or ankyrin. HS is characterized by hemolytic anemia, splenomegaly, and the presence of prominent spherocytes in the peripheral blood. Spherocytes are the result of *conditioning* of the erythrocytes in the spleen, during which reticuloendothelial cells remove portions of the abnormal membrane that are caused by the disordered cytoskeleton. Spherocytes reflect membrane loss that decreases the membrane-to-cytoplasm ratio. Because a high membrane-to-cytoplasm ratio is responsible for the flexible, biconcave shape of the normal erythrocyte, the erythrocyte loses its biconcave morphologic characteristics and assumes a spherocytic shape with loss of membrane. Spherocytes are less flexible and may be destroyed in the microvasculature. The laboratory finding characteristic of HS is increased osmotic fragility, which is caused by the loss of distensibility associated with a decrease in surface membrane. HS is usually a mild disorder with well-compensated hemolysis. Patients typically have exacerbations during infections or when given marrow-suppressing medication. Patients with significant hemolysis should receive folate supplementation. Many patients require cholecystectomy for pigment stones. Severe, symptomatic anemia is treated with splenectomy.

Hereditary elliptocytosis (HE) is caused by dominantly inherited mutations affecting the interactions between membrane proteins and underlying cytoplasmic proteins. The most common abnormalities affect the interactions with spectrin and protein 4.1, which causes the RBCs to assume an elliptical shape. As in HS, patients usually have mild hemolysis and splenomegaly.

Hereditary pyropoikilocytosis (HPP) is a rare recessive disorder that is frequently caused by the inheritance of two different membrane disorders (e.g., one allele for HS and one for HE). Patients have severe hemolysis with microspherocytes and elliptocytes on the smear. As with HS, treatment for symptomatic anemia in HE and HPP is splenectomy.

More information on hemolytic anemias caused by inherited membrane disorders can be found in Chapter 161, "Hemolytic Anemias: Red Cell Membrane and Metabolic Defects," in Goldman-Cecil Medicine, *25th Edition.*

TABLE 47-7 CONGENITAL RED BLOOD CELL MEMBRANE ABNORMALITIES

CONDITION	ABNORMAL MEMBRANE PROTEINS	INHERITANCE
Spherocytosis	Spectrin, ankyrin, band 3, protein 4.2	Autosomal dominant Recessive (rare)
Elliptocytosis	Spectrin, protein 4.1	Autosomal dominant Recessive (rare)
Pyropoikilocytosis	Spectrin	Recessive
Stomatocytosis	Sodium channel permeability defect	Autosomal dominant

Acquired Membrane Abnormalities

Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal disease that is associated with an abnormality of complement regulation. Normal erythrocytes are protected from complement-mediated cell lysis by the presence of membrane proteins, including delay-accelerating factor (DAF or CD55) and membrane inhibitor of reactive lysis (MIRL or CD59). Both these proteins are members of a family of proteins that are anchored to the membrane by a glycosyl phosphatidylinositol (GPI) anchor. Patients with PNH have clonal mutations in phosphatidyl inositolglycan A (PIG-A), the enzyme required for synthesis of GPI. These mutations arise in the hematopoietic stem cell, and all hematopoietic cells lack GPI-anchored proteins. Absence of GPI-anchored proteins from erythrocytes renders them susceptible to complement-mediated lysis. The diagnosis can be made by flow cytometric documentation of the absence of CD55 or CD59 on the surface of RBCs or leukocytes.

PNH is a clonal stem cell disorder with several unique characteristics. Patients suffer from episodic acute intravascular hemolysis with a release of free hemoglobin that results in the hemoglobinuria for which the disease is named. Patients are also susceptible to venous thrombotic complications, including Budd-Chiari syndrome, portal vein thrombosis, cerebrovascular thrombosis, and peripheral veins. The disease is associated with a risk for development of myelodysplasia, myelofibrosis, acute leukemia, or aplastic anemia. Furthermore, patients with aplastic anemia who respond to immunosuppressive therapy frequently develop PNH-like clones. In the past, treatment has been largely supportive. However, treatment with eculizumab, a monoclonal antibody that binds to the C5 component of complement, has been shown to reduce hemolysis, transfusion requirements, and thromboembolic events in this disease. Young patients should be considered for allogeneic stem cell transplantation.

Spur Cell Anemia

Spur cells (acanthocytes) are cells with abnormal membrane morphology found in patients with advanced liver disease, severe malnutrition, malabsorption, or asplenia. The membrane acquires protrusions as a result of the presence of abnormal lipids. The changes may be associated with mild hemolysis, although in patients with advanced liver disease, it is difficult to distinguish hemolysis from hypersplenism. Similar changes may be observed in patients with abetalipoproteinemia.

Hemolytic Anemias Caused by Disorders of Erythrocyte Enzymes

Glucose-6 Phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase (G6PD) is a critical enzyme in the hexose monophosphate shunt pathway. By maintaining intracellular stores of reduced glutathione, it protects erythrocytes from membrane and hemoglobin oxidation (Fig. 47-4). The gene for G6PD resides on the X chromosome, and therefore almost all patients with G6PD deficiency are male. Most G6PD mutations are found in African and Mediterranean populations, most likely because they confer resistance to malaria.