liver transplantation (e.g., for end-stage liver disease and portal hypertension) may help to decrease spleen size and decrease platelet trapping.

Platelet Destruction

One of the first major considerations in thrombocytopenia believed to be caused by platelet destruction is whether such destruction is due caused by immune mechanisms (e.g., antibody-mediated platelet clearance) or nonimmune mechanisms (e.g., microangiopathic processes). This division is important because the pathophysiology, diagnosis, and treatment of these two types of platelet destruction are widely divergent.

Immune-Mediated Platelet Destruction

Immune platelet destruction typically refers to antibody-mediated clearance. Platelet destruction can be further divided into autoimmune forms (i.e., antibody against self-antigens) and alloimmune forms (i.e., antibody against nonself-antigens). Autoimmune thrombocytopenia is the most commonly encountered form of immune-mediated platelet destruction. It may be a primary disorder directed only at platelets or a secondary complication of another autoimmune disease, such as systemic lupus erythematosus. Alloimmune-mediated platelet destruction is rare and is usually encountered only in neonates as a result of maternal antibodies formed against fetal platelet antigens or in chronically transfused individuals, who form alloantibodies against foreign platelet antigens.

In autoimmune and alloimmune thrombocytopenia, immune platelet destruction is caused by increased levels of polyclonal antiplatelet antibodies directed against platelet membrane glycoprotein receptors, most often cryptic neoepitopes of glycoprotein IIb/IIIa (GPIIb/IIIa) and less commonly glycoprotein Ib (GPIb) or human leukocyte antigens (HLAs). Coating of the platelet with these antibodies leads to opsonization of platelets by Fc receptors on cells of the reticuloendothelial system (RES). Antibody-coated platelets are cleared by the spleen and, to a lesser extent, by the liver.

These disorders involve a dramatic increase in marrow platelet production reflected by increased numbers of marrow megakaryocytes. The younger platelets produced have relatively high granule contents, providing increased hemostatic function. Bone marrow examination for increased or normal megakaryocyte numbers is the traditional means of distinguishing platelet destruction from decreased production. However, increased percentages of reticulated platelets are associated with destructive, especially immune-mediated, thrombocytopenia and may be sufficient for diagnosing platelet destruction.

Thrombocytopenia resulting from immune clearance may be severe, and platelet survival is often reduced from the normal 7 to 10 days to less than 1 day. Despite severe thrombocytopenia, serious bleeding or hemorrhagic death is uncommon, partly because the function of young platelets is increased and partly because the number of circulating platelets required to maintain vascular integrity is relatively low, estimated at 7100/μL per day.

Immune Thrombocytopenic Purpura

In children, acute ITP is often preceded by a viral infection such as varicella. Patients with ITP exhibit petechial hemorrhage and mucosal bleeding, and platelet counts are often lower than 20,000/μL. The blood smear shows large platelets but no other abnormal cells such as blasts, which accompany childhood leukemia. The bone marrow has increased or occasionally normal numbers of megakaryocytes. The diagnosis of ITP is partly made by exclusion. Fever, organomegaly, pancytopenia, lymphadenopathy, or abnormal peripheral blood cells should prompt an evaluation for malignant disease, such as leukemia, neuroblastoma, Wilms' tumor, or other bone marrow disorders.

Laboratory tests may complement the clinical evaluation but are not required to make the diagnosis of ITP. Tests may demonstrate an increased percentage of reticulated platelets in the peripheral blood or detect platelet autoantibodies in serum or on the platelet (i.e., platelet-associated immunoglobulin). Assays of platelet-associated antibodies, although sensitive, are not specific for ITP because levels of immunoglobulins that bind nonspecifically to platelets are often increased in patients with thrombocytopenia due to liver disease or human immunodeficiency virus (HIV) infection. Techniques that measure serum antibodies to specific platelet glycoproteins have greater specificity but are relatively insensitive. An increase in mean platelet volume is also a relatively insensitive indicator of destructive thrombocytopenia, in part because of the wide range of normal values. An increase in the reticulated platelet percentage is consistent with increased platelet destruction but cannot distinguish between ITP and other causes of platelet destruction such as heparin-induced thrombocytopenia (HIT) and thrombotic thrombocytopenic purpura (TTP) (see Chapter 54).

Acute ITP in children can resolve without therapy, but clinicians may prefer to treat children with steroids or intravenous immunoglobulin (IVIG), particularly in severe or complex cases. IVIG therapy for ITP is thought to work by three mechanisms. First, high immunoglobulin G (IgG) concentrations block Fc receptors on phagocytes of the RES and on cellular effectors of antibody-dependent cytotoxicity. Second, infusion of IgG increases the fractional rate of IgG catabolism and thereby increases the destruction of antiplatelet IgG in direct proportion to its concentration. Third, clearance of antiplatelet immunoglobulin may increase through anti-idiotypic effects (i.e., generating an immunologic response to the ITP antibodies).

More than 80% of children with acute ITP have a rapid remission, and ITP does not recur. A subset of 10% to 20% of children eventually develops recurrent thrombocytopenia (i.e., chronic ITP); however, more than 70% of them respond completely to splenectomy. For those with chronic courses after splenectomy, episodic IVIG, Rh immunoglobulin, and in severe cases, immunotherapy with rituximab (Rituxan) are used. Hemorrhagic deaths are rare in acute childhood ITP (<2%), but mortality rates of 2% to 5% are associated with chronic, refractory ITP.

The diagnosis of ITP in adults, as in children, is made largely by exclusion, but acute ITP in adults rarely remits spontaneously, and it evolves to chronic ITP in more than 50% of cases. Petechial hemorrhage and mucosal bleeding are accompanied by platelet counts commonly lower than 20,000/μL and often as low as 1000 to 2000/μL. Fewer than 10% of adults with ITP die of hemorrhage.

ITP in adults may be associated with diseases such as HIV or hepatitis C infection. ITP may be the initial manifestation of HIV