Childhood Immune Thrombocytopenic Purpura: Diagnosis and Management

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KEYWORDS

• Immune thrombocytopenic purpura • Immunoglobulin G
• Intravenous anti-D • Combined cytopenias • Splenectomy

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by a low circulating platelet count caused by destruction of antibody-sensitized platelets in the reticuloendothelial system.[1] ITP can be classified based on patient age (childhood versus adult), duration of illness (acute versus chronic), and presence of an underlying disorder (primary versus secondary). Persistence of thrombocytopenia, generally defined as a platelet count of less than 150×10^9/L for longer than 6 months, defines the chronic form of the disorder. Secondary causes of ITP include collagen vascular disorders, such as systemic lupus erythematosus (SLE); immune deficiencies, such as common variable immunodeficiency (CVID); and some chronic infections (eg, HIV and hepatitis C).

This article focuses on the diagnosis and management of children (under 18 years of age) who have acute and chronic ITP. Emphasis is placed on areas of controversy and new therapies.

PATHOPHYSIOLOGY

The pathophysiology of ITP increasingly is understood better (reviewed by Cines and Blanchette.[1]) Not surprisingly, it is complex with involvement of many players in the human immune orchestra, including antibodies, cytokines, antigen-presenting cells, costimulatory molecules, and T and B lymphocytes (including T-helper, T-cytotoxic, and T-regulatory lymphocytes). Current knowledge is summarized later.

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A key element in the pathophysiology of ITP is loss of self tolerance leading to the production of autoantibodies directed against platelet antigens. Evidence for an ''antiplatelet factor'' in the plasma of subjects who have ITP was provided in a seminal report from Harrington and coworkers[2] in 1951. The investigators demonstrated that the infusion of plasma from subjects who had ITP into volunteers induced a rapid fall in platelet count and a clinical picture that mimics ITP. The ''antiplatelet factor'' subsequently was confirmed as an immunoglobulin.[3] Now it is known that the autoantibodies in patients who have ITP mostly are of the IgG class with specificity against platelet-specific antigens, in particular, glycoproteins IIb/IIIa and Ib/IX. Unfortunately, accurate detection of platelet autoantibodies is difficult and not available routinely in most clinical hematology laboratories; clinicians should be aware that indirect platelet autoantibody tests (tests that detect free autoantibodies in the plasma) are inferior to direct tests (tests that detect platelet-bound autoantibodies) and that even with the best direct tests performed in expert immunohematology laboratories, the positivity rate in patients who have well-characterized ITP does not exceed 80%.[4] A negative platelet antibody test, therefore, does not exclude a diagnosis of ITP. For this reason, platelet antibody testing is not recommended as part of the routine diagnostic strategy.[5]

It is increasingly clear that cellular immune mechanisms play a pivotal role in ITP.[1] The production of antiplatelet antibodies by B cells requires antigen-specific, CD4-postive, T-cell help (**Fig. 1**). It also is possible that in some ITP cases, cytotoxic T cells play a role in the destruction of platelets. A possible sequence of events in ITP is as follows. A trigger, possibly an infection or toxin, leads to the formation of antibodies/immune complexes that attach to platelets. Antibody-coated platelets then bind to antigen-presenting cells (macrophages or dendritic cells) through low-affinity Fcγ receptors (Fcγ RIIA/Fcγ RIIIA) and are internalized and degraded. Activated antigen-presenting cells then expose novel peptides on the cell surface and with costimulatory help facilitate the proliferation of platelet antigen-specific, CD4-positive, T-cell clones. These T-cell clones drive autoantibody production by platelet antigen-specific B-cell clones. As part of the platelet destructive process in ITP, cryptic epitopes from platelet antigens are exposed, leading to the formation of secondary platelet antigen-specific T-cell clones, with stimulation of new platelet antigen-specific B-cell clones and broadening of the immune response. The autoantibody profile of individual patients who have ITP reflects activity of polyclonal autoreactive B-cell clones derived by antigen-driven affinity selection and somatic mutation.

Although increased platelet destruction clearly plays a key role in the pathogenesis of ITP, it is now recognized that impaired platelet production also is important in many cases. In adults, as many as 40% of ITP cases may have reduced platelet turnover, reflecting the inhibitory effect of platelet autoantibodies on megakaryopoiesis.[6] Studies of platelet kinetics in children who have ITP are limited but it is possible that a similar situation exists. There also is evidence that platelet autoantibodies may induce thrombocytopenia by inhibiting proplatelet formation.[7] Circulating thrombopoietin (TPO) levels in patients who have ITP typically are normal or increased only slightly, reflecting the normal or only slightly reduced TPO receptor mass in this acquired platelet disorder. In contrast, TPO levels are high in inherited platelet production disorders, such as thrombocytopenia-absent radii or congenital amegakaryocytic thrombocytopenia.[8] TPO testing generally is not available, but these observations have led to the question of whether or not TPO or molecules mimicking TPO may increase platelet production and be a new treatment strategy in ITP. Several such agents currently are in clinical trials.