Diagnosis and Management of Autoimmune Cytopenias in Childhood

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KEYWORDS

- Autoimmune hemolytic anemia • Immune thrombocytopenia
- Autoimmune neutropenia • Evans syndrome
- Autoimmune lymphoproliferative syndrome

KEY POINTS

- Most children with autoimmune cytopenias have idiopathic disease with no secondary cause and enter a spontaneous remission with time.
- Chronic or multi-lineage disease should prompt testing for secondary causes of autoimmune cytopenias, including human immunodeficiency virus, systemic lupus erythematosus, autoimmune lymphoproliferative syndrome (ALPS), and common variable immune deficiency.
- First-line treatments typically include corticosteroids and intravenous IgG. Second-line treatments vary depending on the cell lineage(s) affected and whether or not there is an underlying cause.
- Corticosteroids can cause significant long-term morbidity; therefore, their long-term use should be avoided, because numerous safe and effective alternatives exist.
- Recent advances have led to targeted therapies for select patients, including the use of thrombopoeitin (TPO) receptor agonists (TPO mimetics) for immune thrombocytopenia and sirolimus for ALPS.

INTRODUCTION

Autoimmune cytopenias are a group of heterogeneous but closely related conditions defined by immune-mediated destruction of hematologic cell lineages, including white blood cells (neutrophils), red blood cells (RBC), and platelets. This destruction can be

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primary or secondary to other illnesses. Primary autoimmune cytopenias, formerly classified as idiopathic, consist of single-lineage destruction, including immune thrombocytopenia (ITP), autoimmune hemolytic anemia (AIHA), and autoimmune neutropenia (AIN), as well as multi-lineage destruction, known as Evans syndrome (ES). Secondary autoimmune cytopenias result from another cause, including medications, rheumatologic disorders, immunodeficiencies, lymphoproliferative disorders, malignancies, or as a complication of organ or hematopoietic stem cell transplant (HSCT). Despite their complex and heterogeneous nature, treatment is relatively straightforward, primarily using drugs that suppress or modulate the immune system. Many patients require no treatment; however, others need multi-agent therapy and occasionally autologous or allogeneic HSCT.

This review focuses on challenges encountered in the diagnosis and management of single-lineage and multi-lineage autoimmune cytopenias in children. New treatments for ITP and autoimmune lymphoproliferative syndrome (ALPS) are discussed as paradigms for the translation of basic science into clinic progress, as thrombopoietin (TPO) mimetics (TPO receptor agonists [TPO-RAs]) and mammalian target of rapamycin (mTOR) inhibitors have revolutionized therapy for these 2 conditions, respectively. With modern genomics, this paradigm will likely be used in the near future for other autoimmune cytopenia syndromes.

PRIMARY AUTOIMMUNE CYTOPENIA SYNDROMES

Most children with autoimmune cytopenias have idiopathic destruction of a single-cell lineage, most commonly idiopathic destruction of platelets (ITP). Primary autoimmune cytopenia syndromes are diagnoses of exclusion. However, in children, single-lineage primary autoimmune cytopenias are more common than secondary autoimmune cytopenias. Thus, the default is often to presume that a child who presents acutely with single-lineage destruction has a primary autoimmune cytopenia. Patients with chronic disease or multi-lineage cytopenias, in contrast, more commonly have a predisposing cause, necessitating a more extensive diagnostic evaluation. Patients with primary ITP frequently have a preceding viral syndrome or other immune trigger, such as vaccination. The key difference is that the triggering event is not a chronic illness or a medication. The distinction between primary and secondary autoimmune cytopenias is becoming blurred as genetic alterations and polymorphisms predisposing patients to autoimmune cytopenias are being identified.

ITP

Primary ITP is a rare, generally benign autoimmune bleeding disorder characterized by isolated thrombocytopenia, defined as a platelet count less than 100×10^9/L in the absence of other causes or diseases that may cause thrombocytopenia. The thrombocytopenia is often severe (with platelet counts $<10 \times 10^9$/L), but life-threatening bleeding is rare.[1] Antibodies are often directed against the 2 most prevalent receptors on the platelet surface, GPIb/IX complex (von Willebrand factor receptor) and the GPIIb/IIIa receptor (collagen/fibrinogen receptor) and are detectable in 60% of patients.[2] ITP is caused by a complex interplay of immune dysregulation involving a shift toward Th1 cells, a decrease in regulatory T-cell (Treg) function/number, and cytotoxic T-cell–mediated direct lysis of platelets and megakaryocytes.[3] Dysmegakaryopoiesis plays a critical role in the development of thrombocytopenia.[4]

In 2011, an international ITP working group recommended changing the terminology to immune thrombocytopenia to reflect that many patients may not have bleeding or