Chapter 3
Presentation and Evaluation of Immune Thrombocytopenia

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Introduction

Thrombocytopenia is a common clinical issue in both pediatric and adult medicine. An assessment of the platelet count is routinely sought when there are clinical signs of excessive bruising or bleeding. In addition, thrombocytopenia may be diagnosed incidentally from a complete blood count (CBC) in an asymptomatic patient. While immune thrombocytopenia (ITP) is one of the most common etiologies for a low platelet count, the lack of a specific and sensitive confirmatory diagnostic test makes it a diagnosis of exclusion. This chapter will review the common clinical presentations of ITP and focus on the approach to diagnosis.

Clinical Presentation

The clinical presentation of ITP varies based on the age of the patient and the severity of the thrombocytopenia. In children, ITP usually has an acute onset and often follows a viral illness that occurred in the weeks prior to presentation, resulting in seasonal peaks for diagnosis in the spring and fall [1]. In adulthood, ITP generally has a more insidious onset. The peak pediatric age is 2–6 years, but ITP can occur at any age. In the first year of life, ITP is atypical and is more likely to become chronic. Similarly, ITP in adolescents often behaves more like adult-onset ITP. In children, males and females are equally affected, unlike adults where the incidence of ITP is two- to threefold higher in females.

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In the setting of newly diagnosed ITP, the patient often presents with petechiae and ecchymoses. Bleeding is a less common presenting symptom of ITP, possibly a result of large, functional young platelets that circulate prior to antibody attack and removal from the circulation [2]. Many studies show that the severity of bleeding does not correlate consistently with the platelet count [3–5]. A recent systemic review of bleeding in ITP showed that intracranial hemorrhage (ICH) is a very rare event in both children (0.4%) and adults (0.6%) [6]. Non-ICH severe bleeding occurred in approximately 10% of adults and 20% of children in the acute presentation with ITP [6]. Significant bleeding is rare and generally occurs only when platelets are $<30 \times 10^9/\mu L$.

History

On the first presentation, a detailed history can assist in determining the etiology of the clinical symptoms (Table 3.1). The bleeding history should document the type, pattern, and timing of bruising and/or bleeding. Common sites of bleeding secondary to abnormal primary hemostasis include predominantly skin and mucocutaneous bleeding (epistaxis, oral, GI bleeding, and menorrhagia). Thrombocytopenia is generally not associated with spontaneous muscle or joint bleeding, so the presence of these findings should instigate additional work-up to assess coagulation factors. The onset and timing of bleeding and its relation to triggers such as surgeries and dental extractions can help to determine the severity as well as the chronicity of the condition.

A review of the family history is also important for patients with thrombocytopenia. Although there is no known genetic cause of ITP, several clusters of ITP in families have been documented suggesting there may be a genetic link [7, 8]. In some cases, multiple family members may be affected with ITP and/or other auto-

Table 3.1 Bleeding history to differentiate causes of thrombocytopenia

Key point	Newly diagnosed ITP	Inherited/genetic thrombocytopenia
Onset of bleeding/bruising	Recent	Early in life
Viral prodrome	Often, especially in children	No
Constitutional symptoms	No	No
History of bleeding with triggers (surgery, dental extractions, minor cuts/trauma)	Usually spontaneous onset of bleeding with no significant past bleeding	Yes, often significant
Evidence of congenital anomalies	No	Sometimes (see Table 3.2)
Consanguinity in parents	No	Sometimes (increased in recessive conditions)
Personal history of low platelet counts	No	Yes
Family members with low platelets	Rarely	Often

Table 3.2 Conditions associated with secondary ITP

Autoimmune disorders	Evans syndrome Autoimmune lymphoproliferative syndrome (ALPS) Systemic lupus erythematosus (SLE)
Immunodeficiencies	Combined variable immunodeficiency (CVID)
Infections	*Helicobacter pylori* HIV Hepatitis C Cytomegalovirus Varicella zoster
Drug effects	Strong evidence for quinine, quinidine, trimethoprim/sulfamethoxazole, vancomycin, penicillin, rifampin, carbamazepine, ceftriaxone, ibuprofen, mirtazapine, oxaliplatin, suramin, glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban, eptifibatide), heparin
Others	Vaccine side effect (MMR) Post-bone marrow or solid organ transplantation Antiphospholipid syndrome (APS)

immune disorders suggesting an underlying immunodeficiency or autoimmune predisposition. More commonly, however, a family history positive for ITP suggests an underlying familial thrombocytopenia that is not immune in nature. Inherited thrombocytopenias should be considered and ruled out in families with multiple people that have low platelets [9] (see Chap. 1).

A detailed review of systems may suggest an underlying condition that may have predisposed to ITP. Common comorbid conditions include primary immunodeficiencies, rheumatologic conditions, and other autoimmune conditions (see Table 3.2). The presence of constitutional symptoms is not in keeping with ITP and may suggest a malignancy. A review of current medications is essential as drug-induced thrombocytopenia may be misdiagnosed as primary ITP. A list of drugs that have been shown to cause immune thrombocytopenia can be found in Table 3.2 and have been reviewed in detail recently [10]. Similarly, a complete vaccination review, including timing of the most recent vaccinations, is important as there is evidence to suggest that ITP may occur subsequent to either natural infection with measles or rubella or after the inoculation for measles, mumps, and rubella (MMR) [11].

Physical Examination

The physical examination serves to document the degree of petechiae and ecchymoses, as well as other types of bleeding, and to ensure that the patient is otherwise well without other abnormalities. In typical ITP, there are no other abnormal physical findings. It is important to confirm the absence of clinically significant lymphadenopathy and hepatosplenomegaly. Familial thrombocytopenias may be associated with specific physical findings related to the causative genetic mutation (Table 3.3).

Table 3.3 Physical findings associated with inherited thrombocytopenias

Condition	Inheritance pattern	Gene implicated	Unique clinical/lab findings (in addition to bleeding symptoms)
Small platelets			
Wiskott-Aldrich syndrome	X-linked	*WAS*	Infections secondary to combined immunodeficiency, autoimmune conditions, eczema, cancer predisposition
X-linked thrombocytopenia	X-linked	*WAS*	None
Normal size platelets			
Congenital amegakaryocytic thrombocytopenia (CAMT)	Autosomal recessive	*MPL*	Pancytopenia/bone marrow failure in childhood
Amegakaryocytic thrombocytopenia with radioulnar synostosis	Autosomal dominant	*HOXA11*	Proximal radioulnar synostosis ± other skeletal anomalies, some with sensorineural deafness
Thrombocytopenia absent radii (TAR)	Autosomal recessive	Unknown	Shortened/absent radii bilaterally
Familial platelet disorder/ AML		*AML1*	Early onset myelodysplasia, acute myelogenous leukemia
Large platelets			
MYH9-related disorders	Autosomal dominant	*MYH9*	Sensorineural hearing loss, glomerulonephritis, cataracts
Gray platelet syndrome	Autosomal dominant and recessive types	Unknown	Alpha-granules absent, making platelets appear grey in blood smear, some develop myelofibrosis
X-linked thrombocytopenia with dyserythropoiesis	X-linked	*GATA-1*	Variable anemia ± evidence of hemolysis, hypercellular marrow with erythro- and myelodysplasia
Bernard-Soulier syndrome	Autosomal recessive	*GP1BA, GPIBB, GP9*	Bleeding due to platelet dysfunction
Velocardiofacial syndrome (DiGeorge)	Autosomal dominant	22q deletion	Dysmorphism, developmental and growth delay, cardiac anomalies, cleft lip/palate, hypoparathyroidism, immunodeficiencies
Paris-Trousseau/Jacobsen syndrome	Autosomal dominant	*11q23 (FLI1)*	Congenital impairment, dysmorphic features, cardiac anomalies, growth issues

Bleeding Assessment

Together, the history and physical examination findings can be incorporated into a bleeding score. As the platelet number is often not well correlated with bleeding severity in ITP, the use of a standardized bleeding score can be helpful to quantify

bleeding symptoms at the time of diagnosis and to monitor over time. A recent systematic review identified ten ITP-specific bleeding assessment tools in the literature, two of which have been validated [6]. In clinical practice, some of these tools are felt to be onerous to administer, and their utility is reserved to assess response to therapies in research studies.

Initial Diagnostic Investigations

The complete blood count (CBC) confirms and quantifies thrombocytopenia. Patients with ITP have an isolated thrombocytopenia with preservation of normal white and red blood cell counts. It is important to ensure that the low platelet count is genuine; automated counters may underestimate platelet number when platelet size is abnormal. The mean platelet volume (MPV) is an indicator of platelet size and may be inaccurate with devices that count giant platelets as red cells or in counters with settings that exclude platelets at both extremes of size from the MPV calculation. Platelet size is variable to large in ITP, and MPV may help to differentiate ITP from inherited thrombocytopenias. The size of the platelets can be confirmed on a blood smear, which can rule out platelet clumping and pseudothrombocytopenia (Fig. 3.1). Other than fewer than expected platelets of normal-to-large size, no additional findings are typical on the blood smear in patients with ITP, but other abnormalities may give clues to inherited thrombocytopenias, such as the Dohle-like inclusions seen in the neutrophils of patients with macrothrombocytes due to

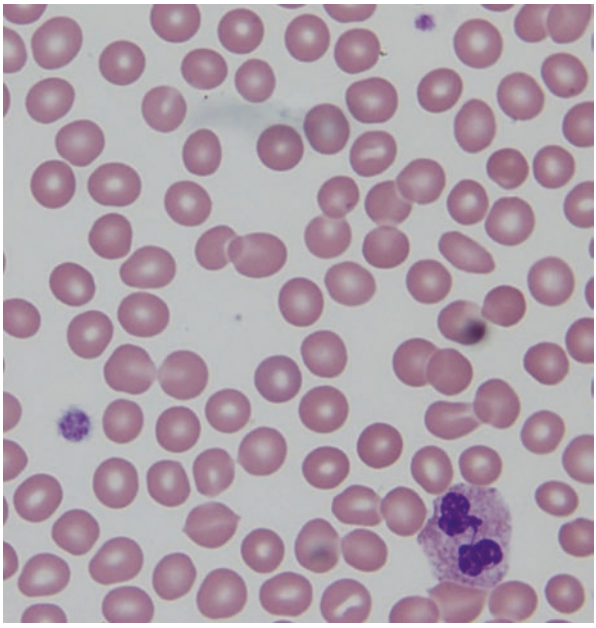

Fig. 3.1 Blood smear in ITP (Image provided by Dr. Jenny Despotovic)

MYH9-related thrombocytopenia. Newer automated machines may report the immature platelet fraction (IPF), which is high in ITP due to high platelet turnover and low in thrombocytopenias due to decreased production. Early studies have suggested that IPF may be useful in deciphering etiology of thrombocytopenia and may be predictive of the development of chronic ITP [12].

In addition to the platelet parameters, other elements of the CBC should be considered. In patients with ITP, the white cell count and differential should be within normal range. Anemia warrants additional consideration, as iron deficiency is prevalent and may be comorbid. In the setting of typical hypochromic, microcytic anemia, iron indices may be sought to confirm iron deficiency anemia. A high MCV and moderate thrombocytopenia should raise the suspicion of possible underlying bone marrow dysfunction, including bone marrow aplasia/dysplasia or inherited bone marrow failure syndromes such as Fanconi anemia. Macrocytic anemia in the setting of thrombocytopenia without a clear etiology warrants bone marrow investigation.

Diagnostic Approach

Taken together, the patient's history, physical examination, and initial investigations are instrumental in considering the differential diagnosis of thrombocytopenia and help in determining if additional testing is necessary. Typical ITP is a diagnosis of exclusion. In addition to the inherited thrombocytopenias mentioned already, other inherited and acquired causes of thrombocytopenia should be considered (see Chap. 1).

Additional Testing for Suspected ITP

The role of additional testing in asymptomatic patients with presumed ITP remains controversial. An International Working Group (IWG) panel of ITP experts published their international consensus on the diagnosis and treatment of ITP in 2010 [13]. Shortly following, the American Society of Hematology (ASH) published an evidence-based practice guideline that summarized the relevant literature using the GRADE system [14]. While these reports are generally in agreement, there are small differences, and their rationales are reviewed here briefly.

The Role of Bone Marrow Testing

The ASH ITP guideline recommends that routine bone marrow examination is not indicated for the diagnosis of typical ITP in children or adolescents, even in those who do not respond to intravenous immunoglobulin (IVIG) therapy. Furthermore,

they suggest that bone marrow examination is not needed prior to initiating steroid therapy or prior to splenectomy for typical ITP in children. Similarly, the ASH guidelines suggest that no bone marrow testing is needed in adults with typical ITP, regardless of the age of the patient [14] (Table 3.4).

Conversely, the IWG panel report suggests a bone marrow examination is recommended in children who show no improvement after 3–6 months with no prior response to therapy. For adult patients >60 years of age, a bone marrow evaluation is recommended at presentation of suspected ITP, based on a higher chance of subclinical marrow dysplasia or malignancy.

Table 3.4 Comparison of recommendations from the ASH ITP guidelines (2011) and the International Consensus Panel (2010) for the investigation of suspected ITP

Investigation	International Consensus Panel (2010)	American Society of Hematology ITP Guideline (2011)
Bone marrow examination for children	• Only when atypical features (not just isolated thrombocytopenia in CBC, systemic features, splenomegaly) • Consider in patients who respond minimally or not at all to first-line therapies • Recommend testing if no improvement in >3–6 months	• Not for patients with typical ITP • Not necessary in cases who fail to respond to IVIG therapy • Suggest not needed prior to steroids or splenectomy
Bone marrow examination for adults	• >60 years and/or systemic symptoms/signs • Prior to splenectomy	• Not at any age for typical ITP
H. pylori testing adults	• Screen with the urea breath test or stool antigen test	• Screen patients who would be treated for a positive *H. pylori* result
H. *pylori* testing—children	• May be of benefit in children with persistent or chronic ITP	• No evidence to test children
HIV and hepatitis C testing	• Recommend testing adults for both at diagnosis • Test children with persistent/chronic ITP in regions where there is a high prevalence	• Recommend testing adults for both at diagnosis
Platelet antibody testing	• Describe the glycoprotein-specific antibody testing as "potentially useful" but do not recommend routine analysis as platelet-associated IgG is elevated in both immune and nonimmune thrombocytopenia	• Insufficient evidence for platelet antibody testing
Screening for autoimmune conditions	• Recommend ANA testing in children with persistent/chronic ITP	• No good evidence to screen all patients with ANA
Screening for immunodeficiency	• Suggest baseline Igs studies in all adult patients with acute ITP and for surveillance in children with persistent or chronic ITP	• Utility of screening all patients with baseline Igs is unclear

Platelet Antibody Testing

Many assays have been developed to measure the antiplatelet antibodies that cause platelet destruction in ITP. Unfortunately, these assays lack sensitivity and/or specificity. The IWG panel describes glycoprotein-specific antibody testing as "potentially useful" but does not recommend routine analysis as platelet-associated IgG is elevated in both immune and nonimmune thrombocytopenia. The ASH ITP guidelines suggest there is insufficient evidence to support the routine use of antiplatelet antibodies as a diagnostic test for ITP in children and adults [14].

Screening Tests for Associated Conditions

Infectious Triggers for ITP: Hepatitis C, HIV, and *H. pylori*

There are no recommended screening tests for infections in children with acute ITP. In adults, both ASH and the IWG expert panel recommend screening adults with new-onset ITP for both hepatitis C and HIV. Treatment of these viral infections is recommended if they are confirmed, as it may lead to resolution of the ITP. The IWG suggests screening children in whom ITP persists >3–6 months in regions there is a high prevalence of these infections.

H. pylori has been implicated in adult ITP, and screening with the urea breath test or stool antigen test has been recommended by the IWG panel. The ASH group also supports screening in adult ITP patients who would be treated for a positive *H. pylori* result. They note that eradication is most successful in patients with less severe ITP and in countries where *H. pylori* is more prevalent. In children, ASH does not recommend *H. pylori* testing for acute or chronic ITP due to a lack of compelling evidence. The IWG group suggests that testing may be of benefit in children with persistent or chronic ITP.

Autoimmune Conditions

Autoimmune hemolytic anemia may occur with ITP, and together they are labeled as Evans syndrome [15]. One study found 22% of all ITP patients tested had a positive direct antiglobulin test (DAT), but the clinical significance of this is unclear [16]. The IWG recommends screening DAT in all patients with ITP. At minimum, a DAT is recommended in patients with anemia, reticulocytosis, and/or evidence of hemolysis. A DAT is also needed prior to therapy with anti-D (see Chap. 4 for more details).

The ASH ITP guidelines do not support screening with antinuclear antibodies (ANA) in children or adults with typical ITP, while the IWG panel suggests that a positive ANA may be a predictor of chronic ITP developing in children [17].

Similarly, the IWG panel suggests screening for antithyroid antibodies/thyroid function as well as antiphospholipid antibodies to be of potential utility in ITP, while the ASH group points out the lack of evidence for the routine use of these tests in the absence of clinical symptoms in both children and adults with ITP.

Immunodeficiencies

Due to an association between combined variable immunodeficiency (CVID) and ITP, it is common practice to check quantitative immunoglobulins in patients with ITP. While the IWG panel supports baseline studies in all patients with acute ITP and for surveillance in children with persistent/chronic ITP, the ASH guideline is less clear, suggesting that the utility of screening all patients is unclear. It is important to consider an assessment of baseline immunologic function prior to embarking on immunosuppressive therapies for ITP.

Summary

The diagnosis of ITP requires a thorough history, careful physical examination, and minimal investigations to rule out other causes of thrombocytopenia. The approach to diagnostic work-up should follow the evidence whenever possible to minimize unnecessary tests and discomfort to the patient. However, it is reasonable to consider baseline screening to detect underlying causes and/or additional antibodies as recommended by expert consensus guidelines.

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