Case Review: Idiopathic Thrombocytopenic Purpura

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Abstract

Idiopathic Thrombocytopenic Purpura (ITP) is defined as a hematologic disorder, characterized by isolated thrombocytopenia without a clinically apparent cause. The major causes of accelerated platelet consumption include immune thrombocytopenia, decreased bone marrow production and increased splenic sequestration. The clinical presentation may be acute with severe bleeding, or insidious with slow development with mild or no symptoms. The initial laboratory tests useful at the first visit to predict future diagnosis were erythrocyte count, leukocyte count, anti-glycoprotein (GP) IIb/IIIa antibodies, reticulated platelets, plasma thrombopoietin level. Treatment should be restricted to those patients with moderate or severe thrombocytopenia who are bleeding or at risk of bleeding. It should be limited in duration unless demonstrated that symptomatic thrombocytopenia persists. Patients with mild, asymptomatic thrombocytopenia, discovered incidentally on a routine blood count, should not be treated. We present a case report on ITP and summarize the key points in the diagnosis and management of ITP.

Keywords: Idiopathic thrombocytopenic purpura; ITP; Platelets; Petechiae; Hematology

Introduction

Idiopathic Thrombocytopenic Purpura (ITP) is defined as a hematologic disorder, characterized by isolated thrombocytopenia without a clinically apparent cause. It is postulated that platelet antibodies opsonizes the platelet membrane resulting in reduced platelet survival by the reticuloentothelial system [1]. The major causes of accelerated platelet consumption include immune thrombocytopenia, decreased bone marrow production and increases splenic sequestration [1, 2]. The clinical presentation may be acute with severe bleeding, or insidious with slow development with mild or no symptoms [1].

The incidence of ITP is 1.6/ 10,000 per year in the United States. Some reports show it is more common in females but others shown no difference in gender distribution [3, 4]. Around 70% to 80% of children experience the acute form of the disease and recover within few weeks or months after diagnosis, whereas most adults have the persistent form and require therapy [5, 6].

Clinical manifestations

The bleeding in ITP is mucocutaneous, manifesting as petechiae, purpura, easy bruising, epistaxis, gingival bleeding, and menorrhagia [1]. ITP remains as a diagnosis of exclusion [1, 7, 8]. In those patients with immune thrombocytopenia, typical clinical findings are missing after a detailed clinical history and physical exam.

Diagnosis of ITP

The American Society of Hematology recommends a panel of tests for initial diagnosis of ITP which includes Complete Blood Count (CBC) and peripheral blood film. No other tests are considered necessary [1, 6]. A similar guideline is followed by British Committee for Standards in Haematology General Haematology Task Force [1, 9]. One study showed that these initial guidelines were not rigorous enough to make an accurate diagnosis of ITP [1, 10, 11]. The initial six laboratory tests useful at the first visit to predict future diagnosis were erythrocyte count, leukocyte count, anti-glyco-

protein (GP) IIb/IIIa antibodies, reticulated platelets, plasma thrombopoietin level [1].

The platelet antibody is a hallmark of the autoimmune nature of ITP. This antibody has a preference to recognize the platelet surface GP IIb/IIIa, but due to the majority of the plasma antibody bound to platelet surfaces rather than in circulation [1, 12], the sensitivity of the test is reduced. The plasma level of the antibodies was not useful in the diagnosis of ITP [1, 13, 14]. This platelet antibody also can affect the proliferation and maturation of megakaryocytes.

Reticulated platelets are young platelet released into circulation containing elevated nucleic acid component, reflecting platelet turnover [1, 15, 16, 17]. Thrombopoietin is one of the main substances controlling the megakaryo-thrombopoiesis, but its levels are not consistently correlated with the absolute number of bone marrow megakaryocytes and platelets [1, 18].

Bone marrow aspiration and biopsy are only performed as a routine if the patient is over 60 years age without a robust response to treatment ($50,000 \times 10^9$/L) [19]. The testing for HIV and/or hepatitis C infection is indicated in at risk populations [19, 20].

Treatment of ITP

The treatment of ITP depends on disease presentation. If the patient is experiencing profound bleeding with very low platelet counts (10,000 to 20,000/UL), initial treatment with IV-Immunoglobulin (IV-Ig) or combined with IV methyl-prednisolone. It may be supplemented with either IV anti-D or with high dose dexamethasone until the platelet count exceeds 50,000/UL. Transfusion of platelet is warranted if life threatening hemorrhage occurs [1, 9].

In non-emergency situations, prednisone (1 - 2 mg/kg/day can be initial treatment), if intolerant to corticosteroids, intravenous IV Ig anti-D can be used [1, 21]. But if platelet remains < 20,000/UL or there is a need for a rapid response, prednisone may be supplemented with IV methylpredniso-lone and/or IV anti-D [1].

More than three quarters of adult patients will fail to achieve a lasting response [1]. The standard of practice for corticosteroids non-responders and platelet counts below 30,000/UL after 4 - 6 weeks of therapy is splenectomy [5], but it may be delayed for up to three years, particularly patients with insidious onset ITP [22].

Patients who have chronic ITP, defined as persisting for more than 6 months, will ultimately need to be treated with other options. Monoclonal antibodies such as Rituximab may also be used. It is postulated that mechanisms of macrophage blockade by opsonized B cells may account for the early responses [1, 23]. Immunosupresants such as Danazol has been shown to improve platelet count in significant number of refractory ITP patients. It is believed to restore suppressor T-cell function and decrease antibodies production

by decreasing the number of available Fc receptors [3, 24]. Cyclosporine, Mycophenolate Mofetil and chemotherapeutic agents such as azathioprine, vinca-alkaloid, cyclophosphamide and interferon have been used with similar success.

Other alternatives are plasma exchange, interferon, colchicine, dapsone, vitamin C, mycophenolate mofetil, protein A Immunoadsorption, thrombopoietin and thrombopoietin like agents. Further studies are warranted for these agents in order to evaluate efficacy, toxicity and adverse effects [1]. Protein A immunoabsorption, thrombopoetin and thrombopoetin-like agents can raise platelet count temporarily. Eradication of H. pylori infection has been reported to improve platelet count in patient with active infection.

We present a case report on ITP. Although not an uncommon entity, there is still much to be learned and this case review will summarize some of the key points in the diagnosis and management of ITP.

Case Report

A 76 year old Hispanic male presented to the emergency department for generalized pain and was found to have low platelet count. The patient was in his usual state of health until 3 weeks prior to presentation when he developed unspecific low back pain and multiple joint pain mainly on his right shoulder. After further questioning patient admitted to having 1 episode of hematuria and epistaxis which were self-limited. Patient denied hematuria, hemoptysis, gingival or gastrointestinal bleeding.

The patient has a past medical history of hypertension, diabetes mellitus type 2, chronic anemia and thrombocytopenia. His past surgical history include left inguinal hernia repair 4 years ago. No significant family history or bleeding disorders were reported. He denied alcohol, drugs or tobacco abuse. His medications were unknown.

Upon arrival to the emergency department, he was alert, awake and oriented, with a blood pressure of 127/72 mmHg, heart rate 100 bpm, temperature 98.4 °F, respiratory rate 18 breaths/min. No orthostatic changes were documented. Physical examination revealed a cooperative and well-appearing man, not in any apparent distress. The pupils were equally round and reactive to light and accommodation. The neck was supple, there were no carotid bruits. No signs of gum bleeding were noticed. The chest was clear to auscultation bilaterally. The heart rate was regular. Auscultation revealed a normal S1 and S2. There were no additional sounds. Abdominal examination revealed no hepatosplenomegaly, bowel sounds were present, no abdominal tenderness, guarding or rebound was found. The extremities revealed no clubbing or edema. Examination of the skin was remarkable for petechiae. Joints were non-tender and non-erythematous, range of movement was normal. The neurologic examination revealed 5/5 motor responses bilaterally in both upper and

lower extremities. No sensory deficits were present. Deep tendon reflexes were 2+ in all four extremities. Guaiac was positive.

Laboratory findings were as follows: Hb 7.8 gr/dL (baseline between 8 gr/dL and 9 gr/dL), Hct 24.4%, WBC: 6.8 x 10³ per uL, MCV: 84 fL, Platelets: 10,400 per UL, PTT: 28.2 sec, PT: 11.8 sec, INR: 1.02. WBC smear was normal. RBC smear showed hypochromic, macrocytic 1+, microcytic 1+, anisocytosis, basophilic stippling. Hemolysis work up was negative.Abdominal ultrasound showed unremarkable spleen and liver.

The patient was admitted to the intensive care unit for close monitoring. Prednisone 80 mg orally daily and intravenous immunoglobulin 30 grams daily for five days were started. Platelets improved to 147,000 per UL and steroids were tapered down, subsequently platelets dropped again to 11,000 per UL. The patient was started again on intravenous immunoglobulin and steroid dose was increased with good response of platelet count.

Discussion

The etiology of ITP may be genetic as well as acquired factors. The pathogenesis is presumed to be related to platelet destruction and/or inhibition of platelet production via the production of specific autoantibodies. The case we presented is only one of the estimated 22 million cases diagnosed each year in the US. Although not an uncommon entity, there is much to be learned in the diagnosis and management of ITP.

Clinical presentation

There is marked variability in the clinical presentation of ITP. Our case was insidious in onset, but it can also be very abrupt and acute. The bleeding manifestations of thrombocytopenia are described as mucocutaneous to distinguish them from coagulation disorders such as hemophilia. Petechia, purpura, and easy bruising are expected in ITP. Less common are epistaxis, gingival bleeding, and menorrhagia. Uncommon findings are GI bleeding, gross hematuria and intracranial hemorrhage [1]. It is important to note that the clinical manifestations of thrombocytopenia vary with patient age. Older patients have more severe and rare bleeding manifestations, such as gastrointestinal bleeding and possibly intracranial hemorrhage secondary to co-morbidities such as hypertension.

Clinically important bleeding does not appear to occur in these patients unless the platelet count is less than 10,000/UL. However, the standard of practice among many physicians is to initiate treatment in adult patients with ITP when the platelet count is less than 30,000/UL. There is no "gold standard" test that can establish its diagnosis. The diagnosis of ITP is in part one of exclusion, requiring that other causes of thrombocytopenia be ruled out. A presumptive diagnosis of ITP is made when the history, physical examination, complete blood count, and examination of the peripheral blood smear do not suggest other etiologies for the patient's isolated thrombocytopenia. The only recommended further tests in such patients are HIV testing in patients with risk factors for HIV infection, and bone marrow aspiration in patients over 60 years of age to rule out myelodysplastic syndrome. In patients with presumed ITP, severe thrombocytopenia, and/or clinical bleeding, urgent hematologic consultation is appropriate and recommended. For asymptomatic patients with modest degrees of thrombocytopenia, consultation is less urgent, but should be pursued in order to establish a baseline, should treatment be required in the future. Contrary to common practice of many physicians, there is still no evidence that antiplatelet antibody studies are important for the diagnosis of ITP.

Treatment

Major bleeding is rare in patients with platelet counts > 10,000/UL. The major goal for treatment of ITP is to provide a safe platelet count to prevent major bleeding and avoid unnecessary treatment of asymptomatic patients with mild to moderate thrombocytopenia. In addition, the efficacy of therapy is uncertain among asymptomatic patients with severe thrombocytopenia. Morbidity from side effects of platelet transfusion exceeds any problems caused by their ITP.

Spontaneous remissions are unusual in adults. In children 70 to 80 percent have complete remission of the disease within six months with no specific therapy. All adults with severe and symptomatic thrombocytopenia are usually treated with glucocorticoids. Adults presenting with mild and asymptomatic thrombocytopenia, with platelet counts greater than 30,000 to 50,000/UL, appear to have a stable and benign course without any treatment. Nevertheless, since spontaneous remissions are unusual in adults with ITP, treatment to increase the platelet count is always initiated in patients with thrombocytopenia severe enough to constitute a risk for bleeding.

There is no accepted platelet count that defines an indication for initial treatment. Patients with initial platelet counts above 30,000 to 50,000/UL, require careful follow-up but no specific initial therapy. Asymptomatic patients with even lower platelet counts may be carefully followed without specific treatment, since major bleeding does not occur unless the platelet count is < 10,000/UL. The decision to treat ITP is based on the platelet count, degree of bleeding, and patient's lifestyle. Corticosteroids, typically prednisone, are the backbone of the initial treatment. When the dose of corticosteroids is reduced or when the treatment is stopped, remission is sustained in only 10 to 30% of cases. Regimens that include dexamethasone may lead to higher rates of sustained remission. Other effective initial treatments include intra-

venous immune globulin and Rh_0 (D) immune globulin for patients who are Rh-positive. Sustained remission with these agents is uncommon. Splenectomy is the traditional second-line treatment for patients who do not have a response to corticosteroids or who do not have a sustained remission with low doses of corticosteroids. In such cases, splenectomy can be curative. Complete or partial remission occurs in more than two-thirds of patients who undergo splenectomy, but the relapse rate is 15 to 25%. The risks associated with splenectomy are small, but patients who have undergone the surgery have a lifelong increased risk of bacterial sepsis.

An array of third-line therapies is available for patients who decline splenectomy and for those in whom surgery is not indicated or must be delayed. Rituximab, the monoclonal antibody against CD20+ B cells, has an overall response rate of 25 to 50%, and many durable responses have been observed with this agent, with relatively few side effects. Other agents that have induced responses when used as third-line treatment include Rh_0 (D) immune globulin, intravenous immune globulin, azathioprine, cyclophosphamide, danazol, alkaloids, dapsone, combination chemotherapy, cyclosporine, and mycophenolate mofetil. The decision to choose one of these agents is usually based on the physician's preference and experience with each agent. With the exception of Rh_0 (D) immune globulin, which is active only in patients with a spleen, these agents can be useful in patients in whom splenectomy fails and who therefore require medical therapy. The major difficulties with many of these third-line therapies are modest response rates and, frequently, a slow onset of action-an effect may not be evident for several months. In addition, bone marrow suppression and an increased risk of infection complicate treatment with many of the immunosuppressive agents. In patients with active bleeding, platelet transfusion can be used. Thrombopoetin like agents can be useful to raise platelet count temporarily [25, 26]. For patient with active H. pylori infection, eradication of this infection should be done [26].

The initial treatment of ITP includes: (1) Treatment should be restricted to those patients with moderate or severe thrombocytopenia who are bleeding or at risk of bleeding; (2) Treatment should be limited in duration unless it is demonstrated that symptomatic thrombocytopenia persists; and (3) Patients with mild, asymptomatic thrombocytopenia, discovered incidentally on a routine blood count, should not be treated.

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