Case Report

REFRACTORY IMMUNE THROMBOCYTOPENIA WITH SUSPECTED EVANS SYNDROME REQUIRING QUADRUPLE THERAPY

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Abstract: A report of a case of recurrent severe form of immune thrombocytopenia (ITP) that failed a re-trial of first-line therapies and required second-line treatments that included a quadruple therapy regimen. This case outlines the aggressive treatment required in treating refractory ITP, but it is also unique because the patient had investigation results suggestive of autoimmune hemolytic anemia (AIHA), raising suspicion of Evans Syndrome.

Key words: Pediatrics; immune thrombocytopenia; Evans Syndrome.

INTRODUCTION Immune thrombocytopenia (ITP) is a common cause of acquired thrombocytopenia in children, second only to chemotherapy-induced thrombocytopenia [1]. Most patients respond well to first-line therapies, however about 25% of initially responsive patients experience a relapse [2]. We report a case of recurrent severe form of ITP that failed a re-trial of first-line therapies and required second-line treatments that included a quadruple therapy regimen. This case outlines the aggressive treatment required in treating refractory ITP, but it is also unique because the patient had investigation results suggestive of autoimmune hemolytic anemia (AIHA), raising suspicion of Evans Syndrome.

CASE PRESENTATION In this case, a 14-year-old boy presented to the emergency room (ER) with a 2-week history of petechial rash, epistaxis, and purpuric bruises. The patient was diagnosed with primary ITP about six years ago following symptomatic severe thrombocytopenia that responded well to intravenous immunoglobulin (IVIG) treatment, and he has since been asymptomatic until now. During the current episode, he developed progressive symptoms over a two-week period (including generalized petechial rashes, epistaxis, and purpuric bruises on his lower limbs), following which he was taken to the ER. Laboratory studies revealed severe thrombocytopenia of 5000/microliter (uL), he was commenced on oral prednisolone and repeat labs with his primary physician (4 days after ER visit) showed worsening thrombocytopenia of 2000/uL. He was subsequently referred to our hospital for expert care. At the hospital, further history-taking revealed strong family history of systemic lupus erythematosus (SLE) in his mother and maternal grandmother. On examination, dried dark blood visualized in nostrils and oral cavity, there was widespread petechial rash noted on the skin especially lower limbs, with a 4-5cm ecchymosis on the anterior aspect of right leg. No jaundice or palpable lymph nodes. Complete blood count on admission showed hemoglobin (Hb) of 9.3g/dl, platelet count of 5000/uL, white blood cell (WBC) of 10,200/uL with normal differentials. Coomb's test was positive, lactate was elevated, and reticulocyte count was 9%. A comprehensive autoimmune panel done was negative. Peripheral blood smear showed severe thrombocytopenia with no platelet aggregate or giant forms, red cells were normocytic and normochromic with some nucleated forms, no WBC blasts or dysplastic forms identified. One unit of platelets was transfused to prevent further bleeds before commencing IVIG, but both measures had no impact with platelet count falling even further to 3000/uL. His Hb also dropped to 7.1g/dl by 3rd day on

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admission and reticulocytes rose to 12%; thus, requiring transfusion with 2 units of blood. High-dose dexamethasone was tried for 2 days but it also failed with no improvement in platelet count. We then commenced second-line therapies with Sirolimus, Rituximab, and Romiplostim, in addition to steroids. Platelet count was monitored daily, and the first sign of response came after 5 days on this regimen when it rose to 11,000/uL, and then to 91,000/uL after 8 days. He was discharged home on daily oral prednisone, sirolimus, and weekly IV rituximab and Romiplostim.

DISCUSSION Immune thrombocytopenia (ITP), formerly known as immune or idiopathic thrombocytopenic purpura, is typically characterized by isolated thrombocytopenia (platelet count <100,000/uL) with normal levels of leukocytes and red blood cells [3]. In this case, the patient met these criteria at his initial diagnosis. The pathophysiology of ITP is the development of antiplatelet antibodies that subsequently result in their destruction, mostly within the spleen [4]. While the underlying mechanism that triggers the development of these antibodies is as of yet unknown, the platelet clearance by splenic macrophages in these patients overwhelms their bone marrow capacity for thrombopoiesis [4]. The result is isolated, often symptomatic, thrombocytopenia with mostly unaffected leukopoiesis and erythropoiesis [4]. Following diagnosis, management of these patients is focused on preventing bleeding through increasing platelet counts and inducing remission [2]. Platelet transfusion is ineffective and is only recommended as a temporary measure to control bleeding risk pending treatment response [1, 5], which was why it was given in this case. First-line therapies include steroids and IVIG, while second-line therapies include use of immune modulators such as rituximab, and thrombopoietin receptor agonists (TPO-RA) such as romiplostim and eltrombopag [1, 5]. Splenectomy is also a treatment option, especially for chronic ITP, as it essentially removes the main site of platelet destruction, but is considered a last resort due to the increased risk of encapsulated organism infection in asplenic patients and the adverse effects of long term antibiotic prophylaxis for such patients.

We presented a patient with an ITP relapse, which had an inadequate response to first-line therapies and was diagnosed as refractory ITP. Refractory ITP is a terminology that has evolved based on the improving therapies available for ITP treatment. An initial definition was persistently low platelet counts following splenectomy and requiring additional treatments to maintain safe platelet count [4]. However, based on improvement in ITP therapeutics, the need for splenectomy, even in severe or chronic ITP, has reduced due to the associated adverse effects as mentioned above. A currently proposed definition of refractory ITP is persistent thrombocytopenia (platelet count < 20,000/uL) requiring continuous therapies to sustain platelet count, or a lack of response to splenectomy [4]. This new definition removes the requirement for splenectomy to have occurred before ITP is considered refractory, and it places the emphasis on the need for continuous therapies to sustain counts. The patient in this case had severe persistent thrombocytopenia and required additional therapies for a prolonged period to achieve remission.

However, other differential diagnoses must also be ruled out in the setting of a refractory ITP diagnosis, these include drug-induced ITP, systemic lupus erythematosus, some infectious diseases, among many others [4]. In this case, the patient had laboratory results that raised suspicion for an alternative diagnosis. His positive coombs test and high reticulocyte count suggested a coexisting autoimmune hemolytic anemia (AIHA), which is strongly suggestive of Evans syndrome. Evans syndrome is a rare diagnosis of exclusion in which there is destruction of at least two bone marrow lineages; the disease tends to be more difficult to treat due to its chronic relapsing and remitting course [5]. It has been reported that some primary ITP patients later develop Evans syndrome later in the course of the disease [5]. In this case, the diagnosis of Evans syndrome could not be definitely made due to a number of confounding factors. Firstly, there was a long period with no follow up between his initial episode and current relapse. Therefore, it is possible that the patient has been in a chronic low platelet state with circulating platelet autoantibodies or drug-induced antibodies that are now cross-reacting with red cells as well [6]. Secondly, the strong family history of SLE raises the possibility of co-existing lupus, especially since ITP secondary to SLE is notorious for difficulty in attaining remission with treatment [7]. Although his autoimmune panel was negative, this could be due to the patient having been on steroids prior to testing, which may have resulted in a false negative result, as steroids can temporarily mask an autoimmune condition [8, 9].

Regardless, treatment of Evans syndrome is similar to the treatment of ITP with first-line therapy consisting of steroids and IVIG, and second-line therapy including immunosuppressants and TPO-RA. However, the rate of relapse following splenectomy in Evans syndrome is significantly high, so it is rarely considered [5].

The patient in our case had improvement in platelet counts and cessation of daily bleeding only upon initiation of

quadruple therapy with sirolimus, romiplostim, methylprednisolone, and rituximab. A discussion of this case may help clinicians in the diagnosis and management of similar cases of refractory ITP.

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