Case Report

Chronic immune thrombocytopenia in a child responding only to thrombopoietin receptor agonist

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ABSTRACT

Immune thrombocytopenia (ITP) is an acquired hematological disease in which the body produces antibodies against its own platelets leading to platelet destruction resulting in isolated thrombocytopenia. Childhood ITP may enter complete remission in the majority of cases within six months from diagnosis. However, 20-30% of affected children may develop chronic ITP (lasting for more than 12 months). First line treatment includes intravenous immunoglobulin (IVIG), corticosteroids or anti-D immunoglobulin. Second line treatment includes splenectomy, immunosuppressive therapy or Rituximab. Recently two thrombopoietin (TPO) receptor agonists (Romiplostim and Eltrombopag) are used to increase platelet count in refractory chronic ITP by increasing platelet production in bone marrow. Here is a case report on an 8 ½ -year- old boy with refractory chronic ITP who failed therapy with IVIG, corticosteroids, splenectomy and Rituximab. He showed excellent response to treatment with TPO receptor agonist (Romiplostim). His platelet count increased from less than 10 x10^3/dl and maintained between 100x103/dl to 200x10^3/dl after few weeks of starting Romiplostim therapy.

Keywords:
Immune thrombocytopenia; Romiplostim; Platelet.

INTRODUCTION

Childhood immune thrombocytopenia (ITP) develops secondary to the production of anti-platelet antibodies that leads to platelet destruction and isolated thrombocytopenia. There is overproduction of megakaryocytes and platelets in the bone marrow as compensatory mechanism to platelet destruction [1-4]. Severe bleeding symptoms are rare [5-8]. The goal of treatment is to raise the platelet count to a safer level in order to prevent serious bleeding like intracranial hemorrhage. The treatment is directed towards neutralizing these antibodies or reducing their production. The first line therapy consists of intravenous immunoglobulin (IVIG), anti-D immunoglobulin or corticosteroids [4,9-11]. In the vast majority of children with immune thrombocytopenia, the disease remits

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within six months with or without treatment. However 20-30% of patients may develop the chronic form of the disease (lasting for more than 12 months). Some of these chronic patients may become refractory, or non responsive to the first line therapy and may experience severe or life threatening bleeding. The second line therapy for these patients is either immunosuppressive therapy, Rituximab or splenectomy [12-17]. Some patients may continue to be refractory to the second line treatment and may continue to have troublesome bleeding. Thrombopoietin (TPO) receptor agonists (Romiplostim and Eltombopag), which increase platelets production in the bone marrow, are used in these cases and produce sustained rise of platelet count and are approved for use in adult patients with ITP in USA, Europe and Japan [18-20]. The present communication reports on a child with refractory chronic ITP, who failed the first line therapy with IVIG and steroids, and second line therapy with Rituximab and splenectomy. He showed excellent response to therapy with TPO receptor agonist (Romiplostim) with sustained normal platelets count.

CASE REPORT

The patient is an 8 ½ -year- old boy. He was first seen in our institution at the age of three years when he developed chronic kidney disease (CKD) secondary to posterior urethral valve (PUV). He underwent surgical resection of the PUV and kept his follow up in pediatric nephrology service for the management of CKD. He had severe hypertension that required three to four drugs to keep it reasonably controlled. He was referred to the Pediatric Hematology Unit (PHU), Department of Pediatrics, College of Medicine, King Saud University, Riyadh at the age of five years, because he was found to have platelet count of 40 $x10^3$/dl (normal count 150 $x10^3$ - 450 $x10^3$) but had no bleeding symptoms. Physical examination was normal, and he had no lymphadenopathy or organomegaly. Complete blood count (CBC) showed normal hemoglobin level and white blood cell count. Peripheral blood smear showed normal morphology and no abnormal cells. He was diagnosed to have immune thrombocytopenia (ITP) and kept his follow up in the hematology clinic. His platelets count was dropping further to less than 20 $x10^3$/dl and at times less than 10 $x10^3$/dl, and he started to have bleeding symptoms in the form of mild nasal and gum bleeds. Because his blood pressure is difficult to control in spite of being on multiple antihypertensive medications, and the possibility of developing intracranial bleeding if the platelet count drops to less than 20 $x10^3$/dl, the plan was made to raise his platelet count to a safer level (i.e. above 20 $x10^3$-30$x10^3$/dl) . Obviously, corticosteroids will not be the first drug to use in the presence of high blood pressure. He was started on IVIG at a dose of 1gm/kg once daily whenever there were bleeding symptoms or platelet count was less than 20 $x10^3$/dl. The dose was repeated twice if platelet count continued to be low. Initially there was good response to this therapy. Unfortunately, he became refractory to repeated doses of IVIG, and platelet count maintained at less than 10 $x10^3$/dl. Bone marrow aspirate and trephine biopsy, performed at this stage, showed markedly increased megakaryocytes and no abnormal cells, findings consistent with the diagnosis of peripheral platelet destruction. He was started on oral prednisone at a dose of 2mg/kg/day for two weeks each time whenever platelet count was less than 10 $x10^3$/dl or if there was bleeding symptoms. Blood pressure was kept under close monitoring during steroid therapy. There was initial response to prednisone, but he later became refractory to prednisone therapy alone and in combination with IVIG. In September 2011, the patient received Rituximab therapy at a dose of 375 mg/m² once weekly for four doses without any significant response. Platelet count continued to be in the range of 10 $x10^3$/dl with occasional bleeding symptoms and the blood pressure continued to be

high in spite of aggressive antihypertensive therapy. Splenectomy was performed in January 2012, hoping to raise the platelet count to a safer level in order to prevent intracranial bleeding, which may occur in the presence of such uncontrolled hypertension. Post-splenectomy platelet count reached up to 500x10^3/dl, but dropped again to less than 10 x10^3/dl. In May 2012 the patient was started on Romiplostim subcutaneously at a dose of 2 microgram/kg once weekly, increasing gradually to 4microgram/kg, which raised his platelet count to a level between 100 x10^3 and 200 x10^3/dl. When last seen in November 2012, he was symptom free and his platelet count was 215 x10^3/dl. No complications to Romiplostim, like flu-like symptoms, fever or headache where noted.

DISCUSSION

Immune thrombocytopenia (ITP) is the commonest platelet disorder in children. The peak incidence is between one and seven years of age. The incidence in children is about 4.0 to 5.3 per 100 x10^3 which is about twice of that in adults [2,4,6]. The disease is usually preceded by viral infection, commonly an upper respiratory tract infection in the previous two weeks. It may also follow vaccination, especially measles, mumps and rubella (MMR) vaccine [21]. The onset is abrupt with symptoms of bleeding under the skin, nasal and gums bleeds. Severe and life threatening bleeding is rare. The reported incidence of severe epistaxis or gastrointestinal bleeding is less than 4%, while intracranial hemorrhage occurs in less than 1% [2-6]. The diagnosis of ITP in children is essentially one of exclusion. The child is usually healthy apart from the presence of bleeding under the skin or mild mucous membrane bleeding. Complete blood count will show isolated thrombocytopenia with normal other blood parameters. Most of the recent guidelines recommend not to treat platelet count alone, but rather to treat the patient condition as a whole [9,22-24]. However, if there is a need to raise the platelet count to a safer level, like in our patient who has difficulty to control hypertension, which may increase the risk of intracranial hemorrhage, IVIG may be used as the first line because it increases the platelets count in 80% of patients and it does so more rapidly than corticosteroids [9,10,22-25]. This patient showed initial response to the IVIG in the recommended dose of 1gm/kg given daily and sometimes repeated twice or three times. Unfortunately, he soon became refractory to such therapy. At this stage bone marrow aspirate and biopsy were examined and showed active bone marrow with increased megakaryocytes, which is consistent with the diagnosis of ITP. The patient was given oral prednisone at a dose of 2mg/kg/day hoping to raise his platelets count to above 20 x10^3-30 x10^3/dl. He showed initial response, but again became refractory to prednisone, given in different doses and regimens, and at times given with IVIG [9,10,22,23]. Rituximab, a chimeric monoclonal antibody against CD20 on antibody-producing cells, is used in the treatment of refractory ITP, and as splenectomy sparing agent with different success rates [14,15,26,27]. Our patient received Rituximab at a dose of 375 mg/m^2 once weekly for a total of four doses. There was no response to Rituximab. The platelets count remained below 10 x10^3/dl and his blood pressure continued to be on the higher side. Splenectomy, is known to cure ITP and is recommended for the treatment of severe chronic and refractory cases in children [9,10,16,17]. This patient underwent splenectomy in January 2012. There was initial response to splenectomy and platelet count reached up to 500 x10^3/dl. Unfortunately, it was non sustained response and platelet count came down to less than 10x10^3/dl again. For long time, the hallmark of ITP was thought to be isolated peripheral thrombocytopenia and compensatory increase in the megakaryocytes and platelets in the bone marrow. Recently, the theory of impaired platelets production as an important factor in the pathogenesis of ITP,

is supported by many evidences in the literature [28,29]. This led to the use of TPO receptors agonists to increase platelets production in the bone marrow so as to overcome the platelets destruction. Two of these agents (Romiplostim and Eltermbopag) are used successfully and have been approved for use in adults with severe ITP who do not respond to the first line treatment [18-20]. In a randomized, double-blind placebo study in children, Romiplostim was found to be very effective in raising platelets count to more than 50 x10^3/dl in 88% of children enrolled in the study. The dose used in this study was 2mcg to 5mcg/kg once weekly [19]. Romiplostim safety is proven in children, but increase in reticulin fibers in the bone marrow is a genuine possibility. Other reported complications are thrombotic episode and congestive heart failure, but these are very rare. Our patient was started on Romiplostim at a dose of 2mcg/kg subcutaneously once every week. When the dose was increased to 3mcg/kg, the platelet count started to rise to more than 50 x10^3/dl, but that rise was not sustained. Romiplostim dose was then increased to 4mcg/dl once weekly. At this dose the platelet count started to be more than 100 x10^3/dl most of the time and reached more than 200 x10^3/dl at other times. The last platelets count (on 24th November 2012) was 215 x10^3/dl. Haemoglobin level and white blood cell count were normal during follow up. The patient had no reported complications.

It can be concluded that Romiplostim may be used in children with severe chronic ITP, who failed other lines of therapy, when there is a real need to increase platelet count to a saver level. However, larger controlled studies are required to further confirm the efficacy and safety of Romiplostim in children.

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