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Case Report

A rare presentation of immune thrombocytopenic purpura

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ABSTRACT

Immune thrombocytopenic purpura (ITP) is defined as a hematologic disorder, characterized by isolated thrombocytopenia without any apparent cause. Some patients may be diagnosed during routine blood investigations or may present with bleeding diathesis. Treatment required for moderate to severe thrombocytopenia or those with bleeding manifestations. We present a case of 43 year old male, sputum positive pulmonary tuberculosis on isoniazid (H), rifampin (R), pyrazinamide (Z), and ethambutol (E) (HRZE) with persistent thrombocytopenia. He developed hepatitis hence isoniazid (INH) and rifampicin were stopped. He had fever, rash, purpura, hematuria and blood tinged sputum with platelet count of 10,000. 4 random donor platelets (RDPs) given. He suffered from mild COVID-19 infection and recovered in 2 weeks but platelets remained low. Bone marrow examination was suggestive of ITP. Inspite of steroid therapy no improvement was seen. Later was treated with injection romiplostim, and started on systemic lupus erythematosus (SLE) regimen for tuberculosis and discharged with regular follow up. Last platelet count being 1,20000/dl, liver function tests normal and now restarted on HRZE.

Keywords: Pulmonary koch's, Immune thrombocytopenic purpura, Megakaryocytes

INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP) is a condition with low platelet count (thrombocytopenia) of unknown cause (idiopathic). As most of the causes are related to antibodies against platelets, it is also known as immune thrombocytopenic purpura.[1] Incidence of ITP is around 50-100 new cases/million/year, with children accounting for half of that amount and median age of adults at diagnosis is 56-60.[1] Early diagnosis and treatment improves prognosis and lifestyle. Steroids are the backbone of treatment. Thrombopoietin analogues help to reduce the bleeding diathesis in dose dependant manner.

CASE REPORT

43 year old male known case of sputum positive pulmonary tuberculosis, diagnosed one month back on HRZE regime was referred from pulmonary OPD in view of persistent thrombocytopenia. Patient was admitted and reviewed. His previous blood investigations were within normal limits. After 15 days of starting isoniazid (H), rifampin (R), pyrazinamide (Z), and ethambutol (E) (HRZE) jaundice developed and HRZE was stopped. Presently he had fever breathlessness and blood streaked sputum since 10 days. Hyperbilirubinemia and thrombocytopenia was present and a diagnosis of AKT induced thrombocytopenia was made. On examination temperature was 101 degree F, pulse-110 beats per minute (bpm), blood pressure-110/80 mmHg, SpO_2 95% on room air. No signs of respiratory distress seen. On physical examination pallor, icterus and bilateral pitting type of pedal oedema were present and cyanosis clubbing lymphadenopathy absent. Small purpuric lesions noted in bilateral lower limbs. On auscultation bronchial breathing and crepitations heard over right upper lung field. Rest systemic examination were normal. Chest X-ray showed right upper lobe cavitatory lesion. His investigations are as follows haemoglobin (Hb) 10.8 g/dl, total leucocyte count

(TLC) 8900/ul, platelet count 10000/ul, total bilirubin 10.8 mg/dl, direct/indirect bilirubin 6.4/4.4 mg/dl, serum glutamic-oxalacetic transaminase/glutamic-pyruvic transaminase (SGOT/SGPT) 108/98 U/l, alkaline phosphatase 134 U/l, serum albumin 2.4 gm/dl, international normalized ratio (INR) 1.8, iron 48 mcg/dl, vitamin B12 1068 pg/ml, HIV/Hbsag/anti HCV negative, thyroid function test (TFT) normal, antinuclear antibody (ANA) by immunofluorescence (IF) negative, and dengue viral markers negative. Rest blood investigations were within normal limits. Microscopic hematuria was present. Sputum studies were repeated again which showed rifampicin sensitive *Mycobacterium tuberculosis*. Ultrasonography (USG) abdomen pelvis showed mild hepatomegaly, no splenomegaly and rest normal. Patient was started on injection ceftriaxone 1 gm intravenous (IV) BD, Injection methylprednisolone 1 gm IV OD, injection human albumin, 4 random donor platelets (RDP) and injection vitamin K. On day 3 platelet count was 11200/ul, total bilirubin 4.4 mg/dl, direct/indirect bilirubin 2.3/2.1 mg/dl, SGOT/SGPT 56/48 U/l, alkaline phosphatase 120 U/l, serum albumin 2.9 gm/dl, INR 1.2, and urine RBC's was 1-2. Inspite of stopping HRZE and treating with steroids no improvement in platelet count was seen. Patient continued to have fever, breathlessness and considering the COVID-19 pandemic, reverse ranscriptase polymerase chain reaction (RTPCR) was sent and came positive. Patient got shifted to COVID ward in our hospital and treated with injection remdesvir and injection dexamethasone 8 mg IV BD. 2 weeks later he came negative, hence shifted back to medicine ward. Thrombocytopenia persisted with platelet count of 13000/ul, and total bilirubin 2.4 mg/dl. Pulmonology review done and advised SLE regime which included injection streptomycin, tablet levofloxacin and ethambutol. Hematology reference was taken and advised to do bone marrow. Under the cover of RDP bone marrow examination was done which revealed mild erythroid hyperplasia with predominantly normoblastic maturation with increased number of megakaryocytes. Hematologist review taken and advised to start, injection romiplostim 250 mcg subcutaneously once a week and vitamin B12 injection. After 2 doses of romiplostim platelet count increased to 80000/ul. Patient was discharged on SLE regime and romiplostim injection. After one month he reported to us with platelet count of 120000 and normalised liver function test (LFT) hence was restarted on HRZE regime along with injection romiplostim.

Table 1: Response of platelet count for romiplostim therapy.

Parameters	Platelet count	LFT (total bilirubin/direct/indirect /SGOT/SGPT/ alkaline phosphatase)
2 weeks of HRZE	10000	10.8/6.4/4.4/108/98/134
After stopping AKT	11200	4.4/2.3/2.1/56/48/120
After recovery from COVID on SLE regimen	13000	2.4/1.8/0.6/52/46/118
After 2 doses of romiplostim injection	80000	1.8/1.1/0.7/50/42/112

DISCUSSION

Immune thrombocytopenic purpura is an acquired disorder wherein there is immune mediated destruction of platelets characterised by mucocutaneous bleeding involving the oral mucosa, gastrointestinal tract or heavy menstrual bleeding, a low platelet count and normal other peripheral blood cells.[2] Rarely massive gastrointestinal (GI) bleeding, hematuria and intracranial hemorrhage may occur.

Bachman and co-workers in 1970 reported thrombocytopenia as rare complication of rifampicin, caused by presence of anti-rifampicin antibodies resulting in platelet destruction.[3]

Recent evidence suggests that stimulus for autoantibody production against platelet membrane glycoproteins IIb-IIIa or Ib-IX is due to abnormal T helper cells reacting with platelet antigens on the surface of antigen presenting cells.

Steroids are first line therapies and those who relapse after steroids can be offered splenectomy. Certain steroid-sparing agents such as azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, and Vinca alkaloids are in use.

A novel approach approved by Food and Drug Administration (FDA) in 2018 for patients with refractory cases of ITP is the use of spleen tyrosine kinase inhibitor fostamatinib 100 mg orally two times daily. Acts by reducing inflammatory response and phagocytosis.[4]

Anti-CD20 antibody rituximab is considered in refractory patients of ITP. It enhances the elimination of B lymphocytes by antibody-dependent cytotoxicity and induction of apoptosis.[5] Usual dose is 375 mg per m^2 every week for 4 doses. Side effects of rituximab include infusion reactions, reactivation of underlying hepatitis, tuberculosis, and rarely fatal progressive multifocal leukoencephalopathy.

Human immuno-deficiency virus (HIV)-associated disease is now considered as most common cause of thrombocytopenic purpura, especially in males between 20 and 50 years of age hence HIV antibodies testing should be done.

Development of first-generation thrombopoietin receptor agonist (TPO-RA) such as PEGylated megakaryocyte growth was eventually discontinued because of neutralizing antibodies that cross-reacted with endogenous

TPO. These were not seen with second-generation TPO-RAs, such as romiplostim, eltrombopag, and avatrombopag.[6]

Romiplostim given as 3 mcg/kg or 5 mcg/kg weekly with dose escalation of 2 mcg/kg every 1–2 weeks until target platelet count is achieved.[7] Eltrombopag given as 25–75 mg oral daily.[8] Side effects of TPO-A are liver toxicity, thromboembolism, and bone marrow fibrosis.[9]

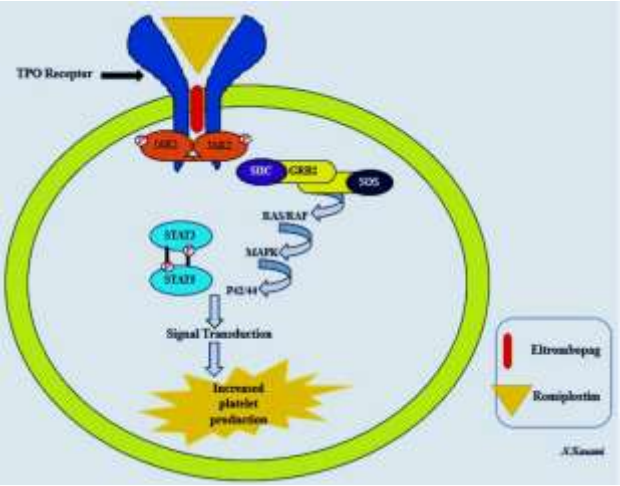

Figure 1: Mechanism of TPO-RA which acts by stimulating TPO receptors of megakaryocytes in bone marrow. JAK2/STAT5 and MAPK are main pathways through which TPO-RAs enhance platelet count by inducing transcription of genes involved in platelet proliferation.[10]

Second-line therapy with rituximab, splenectomy, or TPO-A is considered in patients when thrombocytopenic persists >3 months or if they become steroid dependent.[11]

Certain limitations in the use of thrombopoietin receptor agonists include the absence of long-term safety studies and they are cost ineffective.[12]

Certain novel agents under trial for treatment of ITP include sutimlimab which inhibits classical complement pathway involved in immune mediated destruction of platelets and Decitabine which is a hypomethylating agent.[13] Defective methylation is considered to be involved in pathogenesis of ITP.[14] Early diagnosis and treatment improves prognosis and lifestyle. Steroids are backbone of treatment. Thrombopoietin analogues help reducing the bleeding diathesis in dose dependant manner. But it should be in our back of our mind that withholding a TPO-RA suddenly can precipitate a rebound thrombocytopenia where the platelet count may drop to life-threatening levels a week or two later.

CONCLUSION

Our patient had presented with persistent thrombocytopenia with bleeding manifestations, initially attributing it to drug (AKT) induced but when no response was seen with stoppage of the drug further investigations were done concluding it to be ITP. Patient and family members should be educated about ITP and their associated bleeding risk and patient should be counselled about the compliance with medical therapy and to avoid certain medications like aspirin and NSAIDS which increases the risk of thrombocytopenia.[15] Due to reduced steroid prescriptions and the new TRAs, the prognosis of ITP has improved significantly in recent years.

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