ORIGINAL RESEARCH PAPER

General Medicine

RELAPSING IMMUNE THROMBOCYTOPENIA IN A MIDDLE-AGED FEMALE - GETTING OVER IT

KEY WORDS: ITP; Portal hypertension; Splenectomy, Eltrombopag, Romiplostim

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ABSTRACT

Immune thrombocytopenia (ITP) is characterized by an autoimmune destruction of platelets and megakaryocytes by the reticuloendothelial system. Usually, it occurs without any obvious stimulus. Very often there could be a history of a viral infection, upper respiratory tract or diarrhoea some three weeks prior. Cross reaction of the antigens produced against platelet membranes cause the destruction, something called Molecular mimicry. Secondary immune thrombocytopenia may coexist with an underlying disease such as Chronic lymphocytic leukaemia (CLL), Systemic lupus erythematosus (SLE), Hepatitis C virus (HCV), Human immunodeficiency virus (HIV), Anti-phospholipid antibody syndrome (APLA), Von Willebrand disease or following exposure to certain drugs such as Heparin or Quinidine. Medical treatment includes Corticosteroids, Intravenous immunoglobulins, Dapsone and Rituximab. Romiplostim, a recombinant fusion protein, and Eltrombopag, a non-peptide, have been approved by the FDA for treatment of Immune thrombocytopenic purpura (ITP) refractory to Corticosteroids and Immunoglobulins. If medical therapy fails splenectomy is considered as surgical management.

INTRODUCTION

Primary immune thrombocytopenia (ITP)) is an autoimmune disorder in which thrombocytopenia is caused by both increased peripheral platelet destruction and reduced bone marrow platelet production. There is no specific laboratory test to establish the disease. The incidence rate was approximately 3.3/100000 per year in adults, most adults about >70% shows a chronic course. {1} Current management for chronic ITP includes corticosteroids, rituximab, thrombopoietin receptor agonists and surgical measures like splenectomy. Bone marrow study is one way of establishing the diagnosis (presence of increased number of megakaryocytes). In most of the cases immunoglobulin G (IgG) antibodies directed against the platelets membrane glycoprotein (GP IIb III a) leads to platelet destruction. The antiplatelet antibody assay is not done unlike HIT and VITT where we go in for a PF4 antibody testing. ITP is said to be chronic when the duration of the illness is more than 6 months. Clinical presentation varies between being asymptomatic to severe bleeding complications. Fatal bleeding rates were as high as 1.62 -3.89 per 100 patient years before 2010 and estimated 5-year mortality rate as high as 47.8% in people > 60 years of age. {2} Corticosteroids are the standard first-line therapy of ITP, with a response rate of 20-30% {3}in adults.

About 60 – 90% relapse when Corticosteroids are tapered in adults. In children the disease is completely cured, much to our satisfaction. Long term complications of Corticosteroids include hypertension, diabetes mellitus, cataract, glaucoma, anasarca and osteoporosis {4}

The Case

A 51-year-old post-menopausal female with a known history of Hypertension, Hypothyroidism and Depressive psychosis was admitted for evaluation of petechial rashes over her arms and thighs. She also had a history of black tarry stools. On examination her BP was 130/80 mmHg, pulse 74/min regular, chest revealed vesicular breath sounds and the heart sounds were normal. Petechial rashes were seen over the left arm, right thigh and upper abdomen. The platelet count was a mere 3000/cumm. All other blood tests were within normal range. She was in immense danger of a potentially life threatening intracranial or retroperitoneal bleed. After an initial exclusion of the various causes of thrombocytopenia, a provisional diagnosis of Acute ITP was made. To confirm our diagnosis a bone marrow aspiration and biopsy was done. Bone marrow biopsy reported it as Acute ITP indeed (presence of an increased number of megakaryocytes). IV Methylprednisolone was given for 5 days along with Single donor platelets, 3 such, and the platelet count rose to above 1 lac. Tab Azathioprine was also started subsequently, and she was discharged on the 7th day of hospitalisation on oral steroids. After 10 days her repeat platelet counts again dropped to 7000 per cubic mm and she had to be readmitted. This time her general examination was unremarkable with few faded petechial rashes over the thigh. Intravenous immunoglobulin 60 gm per day was started and this was given for 2 days. Along with this Tab Azathioprine 50 mg once daily and Tab Eltrombopag 50 mg od were also added. The latter is a thrombopoetin receptor agonist. Subsequently platelet values increased to 1.32 lacs, and she was discharged a second time in a stable condition. She was advised to take another opinion from the department of haematology at CMC VELLORE. There she was continued on the same drugs advised by us minus the Eltrombopag and advised to switch over to Sirolimus if ever the platelet count dropped below 50000/cumm. Sirolimus happens to be a time old drug used in organ transplants- it is now fast emerging as perhaps a first line therapy for Acute ITP. The last reported platelet count was 1.24 lacs with no rashes anywhere on the body.

Investigation reports

Table 1

Test	Result	Unit	Reference	Date
Haemoglobin	11	gm/dl	11.5-16.5	15-05-2023
Total Leucocyte Count	4100	per cumm	4000-11000	15-05-2023
Platelet Count	2.72 LACS	per cumm	150000-410000	15-05-2023
Total Bilirubin	0.58	mg/dL	0.2-1.0	15-05-2023
ALT	38.3	U/L	0-45	15-05-2023
AST	22.9	U/L	0-35	15-05-2023
ALP	61.5	U/L	53-141	15-05-2023
Serum Creatinine	0.85	mg/dL	0.5-1.5	15-05-2023
Haemoglobin	9.2	gm/dl	11.5-16.5	05-05-2023
Platelet Count	1.32 LACS	per cumm	150000-410000	05-05-2023

Serum Sodium	134	mEq/l	136-146	03-05-2023
Serum Potassium	4.4	mEq/l	3.5-5.5	03-05-2023
Platelet Count	82000	per cumm	150000-410000	26-04-2023
Platelet Count	73000	per cumm	150000-410000	24-04-2023
Platelet Count	1.02 lacs	per cumm	150000-410000	22-04-2023

Table 2

TEST	RESULT	UNIT	REFERENCE	DATE
Platelet Count	114000	per cumm	150000-410000	29-05-2023
Platelet Count	272000	per cumm	150000-410000	15-05-2023
Platelet Count	132000	per cumm	150000-410000	05-05-2023
Platelet Count	82000	per cumm	150000-410000	26-04-2023
Platelet Count	73000	per cumm	150000-410000	24-04-2023
Platelet Count	102000	per cumm	150000-410000	22-04-2023

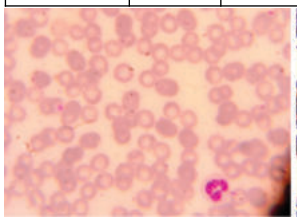

Figure 1 : Leishman stain) – one large platelet seen in center of the field

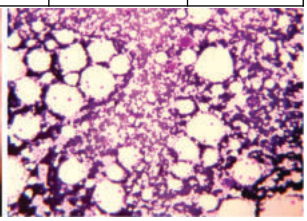

Figure 2 : Bone marrow aspiration (Leishman stain) – Hematopoietic cellular elements with mostly of megakaryocytes of varying sizes.

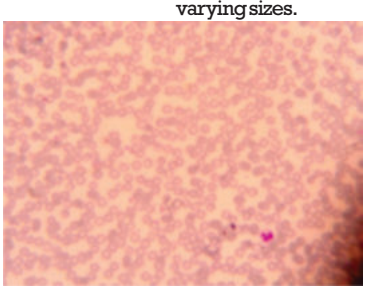

Figure 3 : (Leishman stain) - Red cells are normocytic & normochromic. Neutrophil with normal morphology. Platelets are not present in clumps

Figure 5 (Leishman stain)–mature megakaryocyte with multi-lobated nuclei, granular cytoplasm. However platelet budding is not seen.

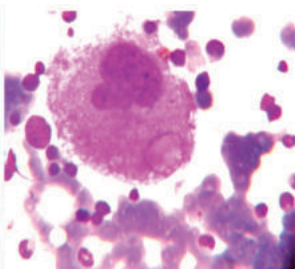

Figure 4 BM Aspiration: (Leishman stain) – Hematopoietic cellular elements with mostly of myeloid cells & immature megakaryocyte with hypo lobated nuclei.

DISCUSSION

Immune thrombocytopenic purpura also known as ITP, is an immune-mediated acquired disease of adults and children characterized by transient or persistent decrease of the platelet count < 100,000 in absence of other disorders associated with thrombocytopenia. The incidence rates of immune thrombocytopenic purpura are between 1.1 and 12.5 per 100,000 children/year in children and between 1.6 and 3.9 per 100,000 adults/year in adults {5} It is twice common in women as in men {6}

ITP can be classified to either primary or secondary. Primary ITP has no clear underlying aetiology, and it is a diagnosis of exclusion. It represents 63% of cases. {7}

Clinical presentation includes symptoms of low platelet count (petechiae, ecchymosis, purpura or conjunctival haemorrhage and gastrointestinal bleed). The International Working Group (IWG) defines complete response (CR) to ITP treatment as a platelet count ≥100 x 10^9/L and absence of bleeding and response (R) as platelet count ≥ 30 x 10^9/L and >2-fold increase in platelet count from baseline and absence of bleeding, both measured on 2 occasions greater than 7 days apart. {8}

The first-line treatment for Acute ITP is Corticosteroids (Prednisone 1 - 1.5 mg/kg body weight) for 4-8 weeks with a tapering course. Corticosteroids act by decreasing capillary permeability, increase platelet production, changing T cell subsets and reducing platelet autoantibody production. [9] The response rate is round 50-75% approximately. The immediate response depends on intensity and duration of treatment {10}

The second-line treatment for ITP is controversial. Meta-analysis of 31 studies done by Arnold et al about the efficacy and safety of Rituximab for adults with ITP showed a CR of 46.3% (based on 13 studies) after treatment {11}

Rituximab is a monoclonal anti CD 20 antibody that decreases anti platelet antibody production by B cells. In some studies, it has been shown to have an overall response rate of 40-70% after 4 weekly doses of 375 mg /m2 {12}. The first dose is always given in an ICU set up because it can cause flash pulmonary oedema.

Other treatment modalities include Anti -RhD immunoglobulin, (administered at a dose of 50 mcg/kg to 75 mcg/kg daily) which can be given as an alternative to immunoglobulin especially for non-splenectomised Rh +patients. It is postulated that it acts by saturating macrophage Fc receptors with anti D coated RBCs which prevents destruction of auto antibody coated platelets. Intravenous immunoglobulins can be given for 1- 2 days (1 gm/kg/day) leading to a rapid rise in platelet count which happened in our case. It neutralises the antibodies produced quickly. Thrombopoietin receptor agonists mimic endogenous TPO function to increase megakaryocyte maturation and platelet production {13} Romiplostim, a recombinant fusion protein can be given subcutaneously once a week (250 mcg). Tab Eltrombopag is a non-peptide which can be taken orally and is indicated for ITP who are refractory to corticosteroids, immunoglobulins and splenectomy {14} It can be started as 25 mg daily and gradually escalated to 50 mg. It can be halted when platelet counts exceed 1.5 lacs. Other than Romiplostim and Eltrombopag -- Avatrombopag and Lusutrombopag have also been approved in Acute ITP. {15}. Fostamatinib is a spleen tyrosine kinase inhibitor which inhibits the inflammatory response and clearance of auto antibody coated platelets by the reticuloendothelial system. Some studies with Tab Sirolimus have shown very promising results for chronic and resistant cases of ITP. Sirolimus is a mammalian target of rapamycin (mTOR) inhibitor shown to inhibit lymphocyte activity. {16} Studies have shown that cytokines secreted from Th1, Th2, Th17 are involved in pathogenesis of ITP. {17}

Th1 cells mainly secrete IFN y, TFN alpha, IL2 mediating local inflammatory response and cytotoxic response. Th2 cells

secrete mainly IL 6, IL10, IL 4 stimulating B cell proliferation to produce antibodies. Levels of activated Th 17 cells were found to be high in ITP which produces high amount of IL 17, IL 21 and IL 22. Sirolimus was found to be associated with reduction in Th2 and Th17, which alleviates platelet destruction. In our patient treatment with Tab Sirolimus along with low dose steroids will be the last line of therapy before splenectomy is considered.

Medicines Under Trial

Rilzabrutinib is an oral, reversible small molecule selective BTK (Bruton's tyrosine kinase) inhibitor that has shown preclinical efficacy in rapidly inhibiting antibody mediated innate immune response as well as antibody production, exhibiting potential for ITP treatment {18}

Bortezomib has been shown to have success in treatment of relapsing ITP in a case report {19}. This is a drug used as a first line therapy in Multiple Myeloma.

Salvage Therapies

Other treatment modalities of ITP include immunosuppressants like Azathioprine, Cyclophosphamide, Vinca alkaloids, Mycophenolate, Dapsone and Danazol are also recommended by experts in the field.

CONCLUSION

Current treatment of Acute ITP in adults involves number of therapies including Corticosteroids and IVIG as well as newer therapies like TPO-RA and Fostamatinib. Management of resistant ITP involves trials with multiple drug therapies. In case of bleeding manifestations, aggressive management is adopted. It is prudent to note that despite the availability of a gamut of new drugs, many of our patients succumbed to a fatal intracranial or retroperitoneal bleed, leaving us to figure out the final panacea for this dreaded disease.

The above-mentioned case is one of our success stories, involving multi-disciplinary opinions, where the patient in question is now living a happy and healthy life, unmindful of her recent turbulent past and looking ahead to a bright future.

Financial Implications – nil

Ethical Considerations - nil

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