Immune Thrombocytopenia (ITP): A Rare Association of Lymphnode Tuberculosis

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Abstract
Although various haematologic abnormalities are known to occur with tuberculosis, association of immune thrombocytopenia with tuberculosis is uncommon. We report a case of retroperitoneal lymph node tuberculosis who presented with ITP. A 76 year old female was admitted to our hospital with oral mucosal bleed and petechial lesions over extremities and abdomen. A diagnosis of immune thrombocytopenia (ITP) was established. Intravenous Anti-D immunoglobin and Dexamethasone therapy was started, but failed to elicit any sustained platelet response. CT abdomen revealed multiple retroperitoneal lymph nodes with central necrosis. Histopathology (HPE) of these revealed caseating lymphadenitis suggestive of tuberculosis. After 2 months of anti-tuberculous therapy, the platelet counts returned to normal and patient was off all therapy for ITP thereby suggesting likely association between tuberculosis and immune thrombocytopenia.

Introduction
Tuberculosis is one of the commonest infectious diseases in India. Various haematologic abnormalities such as anaemia, leucocytosis, monocytois, lymphopenia, leucopenia, thrombocytopenia, thrombocytosis, leukemoid reactions and pancytopenia have been described in tuberculosis1 but immune thrombocytopenia (ITP) as the only presenting feature of tuberculosis is extremely rare with few published reports.2,3

Case Report
A 76 year old female, known long standing diabetic and hypertensive on regular treatment, was admitted to our hospital with haemorrhagic bullae in oral cavity and extensive petechial lesions over lower limbs and abdomen. There was no history of any haematologic disorder or liver disease or significant history of any medication in the past apart from her usual anti-diabetic and anti-hypertensive medications.

The initial total leucocyte count was 6890/cmm with differential count as follows: neutrophils-57%, lymphocytes 33.5%, monocytes 7.5%, eosinophils 1.9%, basophils
0.1%. Haemoglobin was 12.1 g/dl; Platelet count on presentation was 1000 per cubic millimeter. Peripheral smear examination was unremarkable apart from paucity of platelets. Liver function tests, renal function tests and serum electrolyte concentrations were normal and chest X-ray revealed no abnormality.

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were within normal limits and direct Coombs test was negative. Iron studies revealed serum ferritin of 120 ng/ml and lipid profile showed triglycerides of 74 mg/dl.

Subsequently, ultrasonography and CT scan of the abdomen (Figures 1 and 2) were done which demonstrated enlarged para-aortic, aorto-caval and retrocaval lymph nodes - most showing central necrosis. Largest lymph node measured 2.6 x 1.7 cm. Bone marrow aspiration and biopsy showed normocellular marrow with adequate megakaryocytes consistent with peripheral platelet destruction. There was no evidence of lymphoma or tuberculosis on bone marrow biopsy.

During the course of her illness, the patient received 6 units of random donor platelets (RDP’s). There was only minimal and transient platelet response to combined modality therapy with anti-rh0 immunoglobulin and high dose Dexamethasone. The patient was started on Eltrombopag (Thrombopoietin receptor agonist) 50 mg OD. Eight days of therapy effectively raised the platelet count to 9 lakhs / cmm. Eltrombopag was then withdrawn.

Subsequently an exploratory laparotomy was performed for biopsy of retroperitoneal lymph nodes. Histo-pathological examination of these lymph nodes revealed wide areas of caseation and scattered granulomas-indicating caseating tubercular lymphadenitis. Anti-tuberculous therapy was instituted with Isoniazid (300 mg) Ofloxacin (400 mg) Ethambutol (600 mg) and Pyrazinamide (1000 mg) and patient was discharged.

Two months following discharge, patient was seen in good health with a platelet count of 3.4 lakhs / cmm. She had no side effects related to anti-tuberculous therapy. She is under regular follow up without any relapse of thrombocytopenia.

**Discussion**

ITP is an acquired disorder in which there is immune mediated destruction of platelets and possibly inhibition of platelet release from megakaryocytes. ITP in children usually presents acutely while in adults it runs a more chronic course, although at times it can have a very abrupt and stormy presentation. Common secondary causes of ITP include auto immune diseases, infections (HIV/hepatitis C) and drugs (rifampicin).

In the present case scenario, following possibilities were considered in differential diagnosis:

1. **Disseminated Intravascular Coagulopathy**: DIC is a complex thrombo haemorrhagic disorder involving fibrinolysis and consumption of procoagulants and platelets. Typically, prolonged coagulation times, thrombocytopenia, high levels of fibrin split products and microangiopathic pathology (schistocytes) on peripheral smears are suggestive findings. In our patient PT and aPTT were normal, thus ruling out DIC.

2. **Thrombotic Thrombocytopenic Purpura (TTP)**: Patients with TTP typically report an acute or subacute onset of symptoms related to neurological dysfunction, anaemia or thrombocytopenia. Fever occurs in approximately 50% of the patients. Peripheral smears reveal moderate to severe schistocytosis. Thus, TTP was ruled out in our patient as there was no evidence of microangiopathic haemolysis.

3. **Evans Syndrome**: Evans syndrome is the co-existence of sequential or simultaneous direct Coombs – positive AIHA (Autoimmune
haemolytic anaemia) in conjunction with immune mediated thrombocytopenia, with no known underlying aetiology. In our patient Evans syndrome was ruled out as haemoglobin level was normal and direct Coombs test was negative.

4. Haemophagocytic Syndrome: It represents a severe hyperinflammatory condition with cardinal symptoms of prolonged fever, cytopenias, hepato-splenomegaly and haemophagocytosis. In addition to pancytopenia, hypofibrinogenaemia and hypertriglyceridaemia are also present, with serum ferritin levels paralleling the course of the disease. Hence in absence of pancytopenia and any palpable organomegaly and presence of normal serum ferritin and triglyceride levels Haemophagocytic syndrome was ruled out.

We therefore decided to investigate her further with a CT scan of abdomen. It revealed retroperitoneal lymphadenopathy with central necrosis. Histopathological study showed caseation suggestive of tuberculosis. In absence of any other convincing cause for severe thrombocytopenia, we postulate a possible association of tuberculosis with her clinical presentation; although it may not be directly causal.

Patients with both pulmonary and extra-pulmonary tuberculosis may demonstrate haematological abnormalities such as anaemia, leucocytosis, monocytosis, lymphopenia, leucopenia, thrombocytopenia, thrombocytosis, leukemoid reactions and pancytopenia but severe thrombocytopenia due to ITP as an association with tuberculosis is extremely rare.

It has been observed that thrombocytopenia in tuberculosis can occur due to

1. A defect in platelet production (marrow infiltration),
2. Tuberculosis induced haemophagocytic syndrome,
3. Side effect of anti-tuberculous therapy or,
4. Immune-mediated platelet destruction.

Drug-induced thrombocytopenia (i.e. as a side effect of anti-tuberculous therapy) develops within 6-7 days in individuals taking drugs for the first time, and within hours in sensitised patients. Some patients may not develop thrombocytopenia for months to years. Further, it has been observed that the platelet count is usually restored within a week of cessation of the offending agent. Corticosteroids have also been used in such scenarios, with intravenous immune globulin (IVIg) or plasmapheresis reserved for life threatening situations.

Our patient did not show any evidence of marrow infiltration with tuberculosis, neither was she exposed to anti-tubercular drugs prior to development of thrombocytopenia. Thus the only plausible explanation is immune mediated platelet destruction associated with tuberculosis. This in itself is exceedingly rare. Anti-tubercular antibodies cross reacting with platelets can be a possible hypothesis for the same.

It is interesting to note that our patient had a fulminant form of steroid and anti-D resistant ITP, necessitating a TPO agonist (Eltrombopag) to achieve response. Eltrombopag is a small molecule Thrombopoietin receptor agonist for oral administration. It interacts with the transmembrane domain of Thrombopoietin receptor (also known as C-MPI) leading to increased platelet production. However, treatment of tuberculosis itself led to complete remission of ITP suggesting some possible association.

ITP and tuberculosis are common diseases in India. A high index of suspicion of tuberculosis may be warranted in patients presenting with ITP as noted in our patient, the ITP may be cured with treatment of tuberculosis.

References