# Immune Thrombocytopenia in Tuberculosis: Causal or Coincidental?

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## ABSTRACT

Immune thrombocytopenia is a relatively rare hematological manifestation in tuberculosis. We report two cases of immune thrombocytopemia, one in sputum positive pulmonary tuberculosis and the other in miliary tuberculosis. Antituberculous drugs and immunosuppressive therapy corrected the thrombocytopenia in both patients. Our case reports stress that tuberculosis should be considered during the evaluation of immune thrombocytopenia, and also highlights the safety of immunosuppressive therapy during active tuberculosis along with antituberculous drugs.

**Key words:** Immune thrombocytopenia, Miliary tuberculosis, Pulmonary tuberculosis

## INTRODUCTION

Tuberculosis (TB) is a major communicable disease in both developing and developed countries. The incidence is on the rise due to multidrug-resistant bacilli and Human Immunodeficiency Virus (HIV). As of 2012 India has the highest incidence of the disease with an estimated 2.2 million cases, accounting for 26% of the global incidence according to the World Health Organization statistics.[1] A wide spectrum of hematological manifestations has been observed in TB, with thrombocytopenia being common in miliary TB and thrombocytosis in pulmonary TB.[2] Thrombocytopenia in TB is usually non-immunological, due to pancytopenia following bone marrow infiltration. Newly diagnosed immune thrombocytopenia in TB is rare and only 27 cases have been reported so far. We describe immune thrombocytopenia in two patients with active pulmonary TB and miliary TB, both of whom recovered completely with immunosuppressants and antituberculous therapy (ATT).

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## CASE REPORTS

### Case 1

The first case is about a 16-year-old boy who presented with high grade fever and cough with mucoid expectoration for 10 days. Examination revealed petechiae over the patient's chest and upper arms. There was no lymphadenopathy or hepatosplenomegaly.

Hemogram showed low platelets (10,000/ cu.mm) and erythrocyte sedimentation rate (ESR) of 42 mm/h. Peripheral smear showed severe thrombocytopenia and no myeloid cells. High resolution computed tomography (HRCT) of lungs showed a cavity in the right upper lobe with surrounding consolidation [Figures 1 and 2]. Sputum for acid fast bacilli (AFB) was positive, and culture grew *Mycobacterium* TB. Ultrasound of the abdomen was normal. Bone marrow aspirate showed normocellular marrow, normal maturation of erythroid and myeloid precursors and increased megakaryocytes [Figure 3]. No hemophagocytic cells were seen. Bone marrow culture for AFB was sterile. Renal function tests, liver function tests, serum fibrinogen, D-dimer, and serum procalcitonin were all within the normal limits. Direct Coombs test, serological tests for Hepatitis B virus, Hepatitis C virus, HIV and antinuclear antibodies were negative.

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A diagnosis of sputum positive pulmonary TB with possible immune thrombocytopenic purpura was made and ATT was begun including Isoniazid, Ethambutol, Pyrazinamide (Rifampicin excluded due to thrombocytopenia, Levofloxacin included). Immunosuppressive therapy was also begun with 1 g of intravenous pulse methylprednisolone for 3 days followed by 40 mg of oral prednisolone once daily. After an initial positive platelet response, platelet counts began to drop. Hence intravenous immunoglobulin was begun (total of 60 g given over 3 days) which led to an improvement in platelet counts. Patient was discharged on ATT and oral prednisolone. Prednisolone was tapered over 6 weeks and stopped. After completion of ATT, patient's sputum was negative for AFB, chest X-ray showed clearing of the shadows and platelet counts were in the normal range.

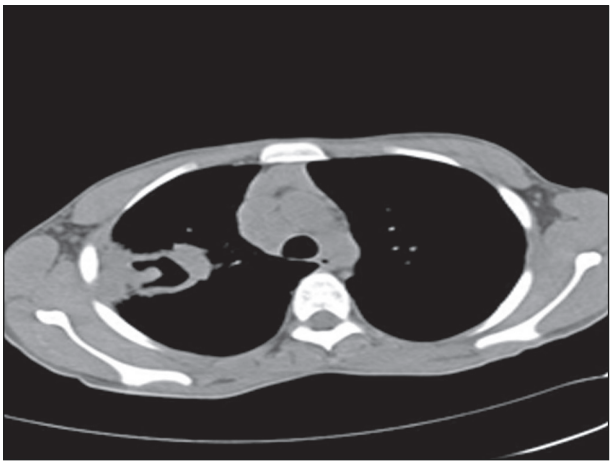

**Figure 1:** Computed tomography of chest shows irregular thick walled cavitary lesion with surrounding air space consolidation in the right upper lobe with ground glass opacity in the posterior segment of right upper lobe

## Case 2

A 19-year-old female patient was admitted with a 1 month history of low grade intermittent fever and cough with scanty sputum. Initially she had fever and thrombocytopenia (60,000/cu.mm) which was evaluated elsewhere and attributed to viral infection. She was referred to our hospital with continuous low grade fever and serial persistent thrombocytopenia (40,000/cu.mm and 48,000/cu.mm). She never had any bleeding tendencies. She appeared ill. Systemic examination was normal.

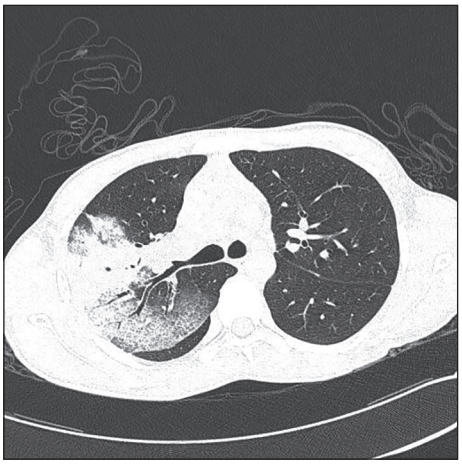

**Figure 2:** High resolution computed tomography of chest shows air space consolidation in right upper lobe with ground glass opacity in the posterior segment of right upper lobe

Hemogram showed thrombocytopenia (42,000/cu.mm) and ESR of 46 mm/h. Peripheral blood smear showed thrombocytopenia and morphologically normal platelets. Repeated blood cultures were negative. Sputum AFB was negative. Secondary causes for thrombocytopenia were ruled out as in the previous case.

Chest X-ray posteroanterior and HRCT of the chest showed miliary mottling [Figure 4]. Meanwhile, the patient developed altered sensorium and headache. Tuberculous meningitis was suspected clinically. Computed tomography of the brain showed mildly dilated lateral ventricles with obstruction. Cerebrospinal fluid analysis showed features of tuberculous meningitis (increased protein, increased cell count with lymphocytic predominance and increased adenosine deaminase of 15 IU/L, normal value <10 IU/L). Bone marrow showed megakaryocytosis and ill-defined granulomas with normal maturation of erythroid and myeloid precursors [Figure 5]. Bone marrow smear was negative for AFB and culture was sterile.

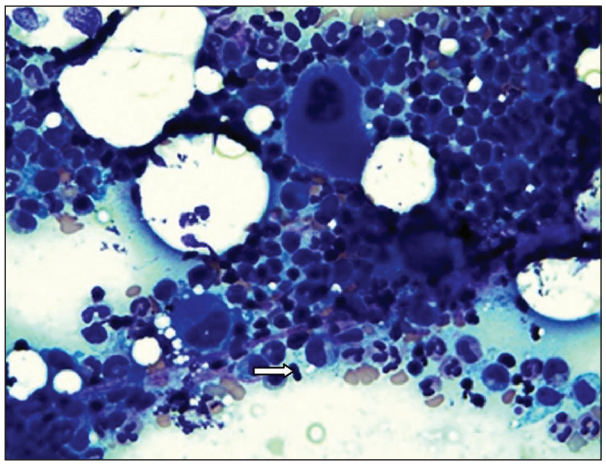

**Figure 3:** Bone marrow aspirate showing immature hypolobulated form of megakaryocytes-white block arrow (Giemsa stain, magnification ×400)

A diagnosis of miliary TB with immune thrombocytopenia was made. ATT including Isoniazid, Rifampicin, Ethambutol and Pyrazinamide was begun along with intravenous dexamethasone 4mg twice daily. The patient improved clinically and was discharged with ATT and prednisolone 1 mg/kg/day. Prednisolone was tapered over 3 months and stopped. After completion of ATT, chest X-ray was clear and platelet counts were within normal range. Temporal profile of case 1 and case 2 [Table 1].

## DISCUSSION

TB has various organ system involvements including the hematological system. Hematological manifestations of TB include anemia, leukocytosis, leucopenia, thrombocytosis, or thrombocytopenia among others.[2] Thrombocytosis is commonly seen in pulmonary TB and thrombocytopenia in miliary TB.[2] Thrombocytopenia in TB may occur owing to defective platelet production in the context of pancytopenia due to bone marrow infiltration, histiophagocytosis, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, immune mediated platelet destruction or as an adverse effect of therapy with rifampicin and isoniazid.[3]

Immune thrombocytopenia is an acquired autoimmune disorder characterized by isolated thrombocytopenia with peripheral blood platelet count <100,000/cu.mm, with or without mucocutaneous bleeding.[4] It is a diagnosis of exclusion. Isolated thrombocytopenia has been reported in 23-43 % of patients with disseminated TB.[5] Immune thrombocytopenia in TB is rare and very few cases have been reported so far.[6-9] These patients presented with constitutional symptoms, cough with hemoptysis and few with mucosal bleeding.

The mechanism of TB-related immune thrombocytopenia is not clear. One theory is that antiplatelet antibodies may be produced by activation of a clone of B-lymphocytes by *Mycobacterium* TB.[10] Another is, *Mycobacterium* TB may share antigen with platelets leading to antiplatelet antibody.[11]

The patient in Case 1 had constitutional symptoms attributable to TB and petechiae with isolated thrombocytopenia. The patient in Case 2 had persistent

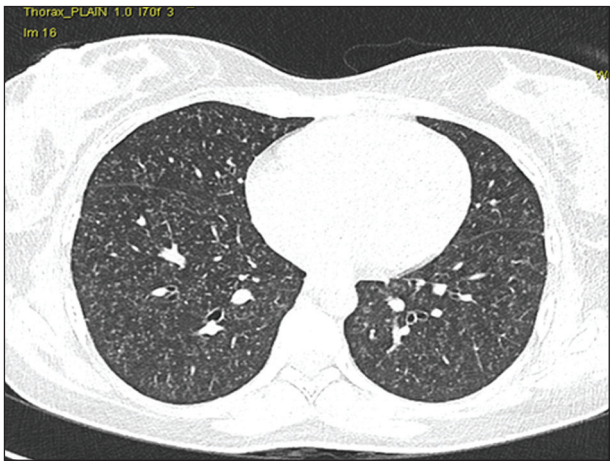


**Figure 4:** High resolution computed tomography of lung shows miliary pattern in bilateral lung fields with few coalescent larger nodules

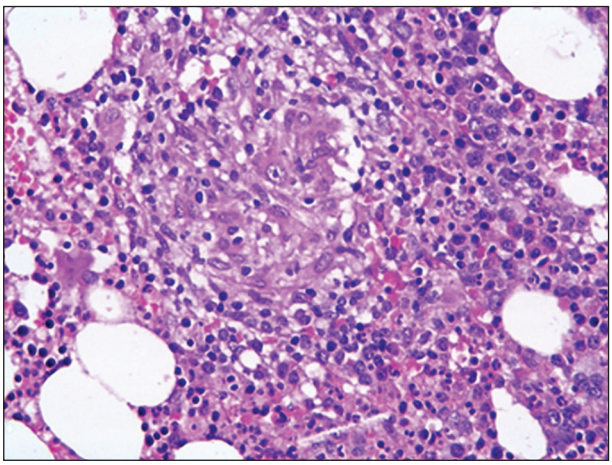

**Figure 5:** Bone marrow biopsy showing epithelioid granuloma (H and E, magnification ×400)

**Table 1: Temporal profile of the patients before and after treatment**

| Time frame | Case 1 | | Time frame | Case 2 | |
|---|---|---|---|---|---|
| | Platelet count (cells/cu.mm) | Treatment | | Platelet count (cells/cu.mm) | Treatment |
| Day of admission | 10,000 | Platelet transfusion | Day of admission | 42,000 | — |
| Day 2 | 13,000 | Platelet transfusion. ATT started | Day 3 | 40,000 | ATT |
| Day 4 | 8000 | ATT with intravenous steroids (methyl prednisolone) | Day 5 | 40,000 | ATT with steroids (injection dexa-methasone) for TB meningitis |
| Day 7 | 20,000 | ATT with oral steroids (prednisolone) | Day 7 | 75,000 | ATT with steroids |
| Day 8 | 10,000 | Intravenous immunoglobulin | Day 10 | 78,000 | ATT with steroids |
| Day 11 | 42,000 | Discharged with ATT and oral steroids | Day 12 | 78,000 | Discharged with ATT and oral steroids |
| Follow-up — 3 months | 240,000 | Steroids stopped. ATT continued | Follow-up — 3 months | 190,000 | Steroids stopped. ATT continued |
| Follow-up — 6 months | 282,000 | ATT completed | Follow-up — 6 months | 320,000 | ATT completed |

ATT: Antituberculous therapy; TB: Tuberculosis

isolated thrombocytopenia during episodes of fever, and miliary TB was diagnosed based on histological and radiological evidence. Normocellular marrow with megakaryocytosis indicates peripheral thrombocytopenia. Secondary causes for immune thrombocytopenia such as drugs, infections, autoimmune conditions and malignancy were ruled out in both cases. Even though granulomas were seen in the bone marrow of the second patient, the absence of pancytopenia excludes bone marrow infiltration as the cause of thrombocytopenia. The immunological basis of thrombocytopenia is evident from the response to steroids and intravenous immunoglobulin. Normalization of platelet counts after completion of ATT suggests TB as the etiology of the thrombocytopenia.

The other cases reported so far have also received similar treatment with steroids, intravenous immunoglobulin and ATT. Tests to detect antiplatelet antibodies were unavailable.

## CONCLUSION

TB-related immune thrombocytopenia is a rare hematological manifestation of a common disease. It may be treated with immunosuppressants along with ATT. TB should be considered as a cause of immune thrombocytopenia in endemic areas and more research is needed to elucidate the pathogenesis of TB-related immune thrombocytopenia.

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