Immune thrombocytopenia and its association with lymph node tuberculosis – A dilemma!

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ABSTRACT

Background: Although various hematologic abnormalities are known to occur with tuberculosis, association of immune mediated thrombocytopenia with tuberculosis is uncommon. Newly diagnosed immune thrombocytopenia in TB is rare; only 27 cases have been reported so far.

Case: We report a case of axillary lymph node tuberculosis who presented with immune thrombocytopenia. An eighteen year old girl was admitted to our hospital with excessive vaginal bleed of one week duration followed by the development of petechial lesions and ecchymosis over legs, hands and mouth. She also had solitary, firm, left axillary lymphadenopathy. A diagnosis of immune mediated thrombocytopenia (ITP) was made from peripheral blood smear and bone marrow examination. Intravenous methylprednisolone (30mg/kg body weight) followed by oral prednisolone (1mg/kg) failed to elicit any sustained platelet response. Fine needle aspiration cytology of the left axillary lymphadenopathy done later revealed tuberculosis. After two weeks of starting anti-tuberculous therapy, the platelet count returned to normal and she was off all therapy for ITP thereby suggesting likely association between tuberculosis and immune thrombocytopenia.

Conclusion: This case report illustrates the causal association between immune thrombocytopenia and tuberculosis.

Key words: tuberculosis, thrombocytopenia, bleeding, purpura, lymphadenopathy

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INTRODUCTION

Tuberculosis is one of the commonest infectious diseases in India. Various haematological abnormalities such as anaemia, leucocytosis, leucopenia, monocytosis, leukemoid reactions, pancytopenia, haemophagocytic activation syndrome have been described in tuberculosis (1), but immune thrombocytopenia (ITP) as the only presenting feature of tuberculosis is extremely rare with few published reports available in literature.

CASE REPORT

An 18 year old girl previously healthy, was admitted to our hospital with history of excessive vaginal bleeding of 1 week duration followed by the appearance of red spots over legs, hands, abdomen, lips and inside the mouth. She also had bleeding from gums 1 day prior to the hospital admission. She did not have fever, joint pains, abdominal pain or jaundice. Prior to the present episode, her menstrual history was normal. She had not taken any medicines known to decrease platelet count. Her general examination revealed pallor, non palpable, non tender, purpura over legs, forearms, hands, lips and inside the oral cavity.

She had single non tender, firm central lymph node (2" X 2") palpable in the left axilla. On direct interrogation, she admitted to have noticed the swelling in the left axilla about 3 weeks before the development red spots. Rest of the physical examination was normal. She was haemodynamically stable. Her systemic examination was normal except for tachycardia. There was no organomegaly per abdomen.

The initial laboratory investigations revealed haemoglobin 5.3 gm/dl, MCV 78fl, RCDW (CV) 14%, white blood cell count 5.3× 109/l with 60% polymorphs, 37% lymphocytes, 2 % monocytes and 1% eosinophils and platelet count of 10 × 109/l. Her peripheral smear was marked by paucity of platelets with no evidence of haemolysis (figure 1). Serum Iron was 28mcg/dl. A bone marrow biopsy revealed mild hypercellularity of all cell lines with normal maturation of myeloid and erythroid precursors. Megakaryocytes were increased in number with normal morphology. No granuloma was detected (figure 3). The coagulation tests like PT (INR), PTT, serum fibrinogen and fibrin degradation products (FDP) were normal. Anti nuclear antibody, dsDNA, rheumatoid factor, direct Coomb's test, serology for HIV l and ll and blood cultures for specific infections were negative. Liver function tests and renal function tests were normal. Mantoux test was 20 mm positive. Her chest x ray and ultrasound of abdomen were normal. ESR was 55 mm 1st hour. FNAC of left axillary lymph node revealed predominantly caseous necrosis with lymphocytes and occasional giant cells. There was no evidence of malignancy (figure 2).

A diagnosis of tubercular axillary lymphadenitis, iron deficiency anaemia with secondary immune thrombocytopenia was made. Before her FNAC report was available, she was treated with methylprednisolone intravenously 30 mg/kg body weight for 3 days followed by oral prednisolone 1mg/kg (40 mg OD) and azathioprine 1mg/kg. Her platelet count, however, hovered between 10,000 to 30,000/cu mm. When the report of FNAC was available, she was

put on WHO Category-I antituberculous drugs-isoniazid, pyrazinamide and ethambutol. Rifampicin was not given as it is known to cause thrombocytopenia.One week after starting antituberculous drugs, her platelet count began to build up and it normalized in 2 weeks (figure 4). Rimpancin was introduced on outpatient basis. She is on regular follow up and has completed 4 months of therapy. Her platelet count when last seen was 1.8Lakhs/cu mm. She is off steroids and is on INH and Rifampicin.

Figure 1 : Peripheral smear showing paucity of mature platelets.

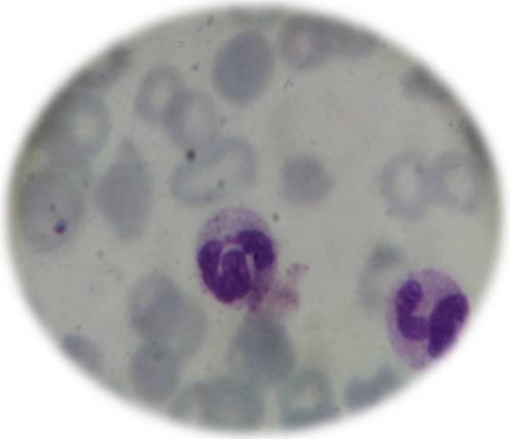


Figure 2: FNAC of lymph node showing predominantly caseous necrosis, occasional giant cells against necrotic background suggestive of granulomatous inflammation.

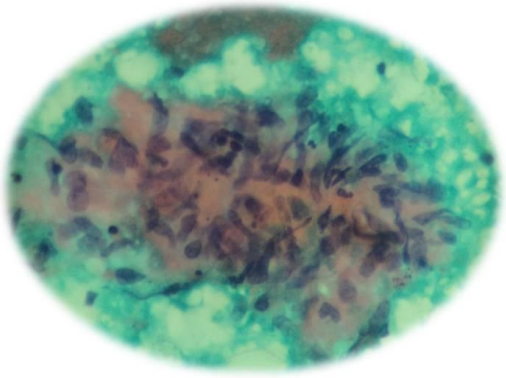


Figure 3 : Bone marrow aspiration showing increased megakaryopoisis and predominanance of mature and immature megakaryocytes.

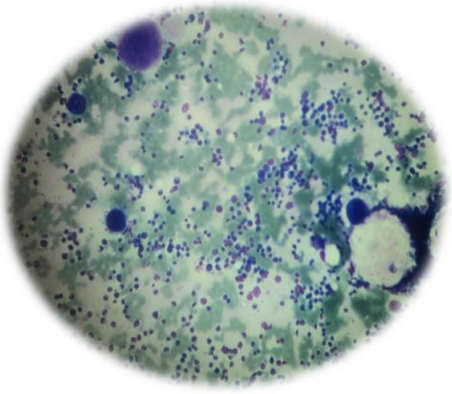
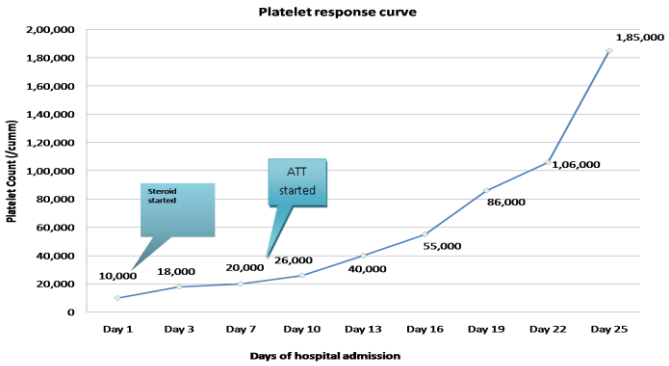


Figure 4 : Platelet response following antitubercular therapy



DISCUSSION

Tuberculosis is one of the world's most challenging communicable diseases. The hematological abnormalities associated with tuberculosis are well recognized. Both pulmonary and extrapulmonary tuberculosis may demonstrate a myriad of haematological abnormalities such as anaemia, leucocytosis, monocytosis, lymphopenia, leucopenia, leukemoid reaction, pancytopenia, haemophagocytic syndrome and thrombocytopenia[1,18] as revealed by comprehensive review of literature.

When thrombocytopenia occurs, it does so most commonly via non-immunologic means, typically manifesting in the context of pancytopenia that develops secondary to granulomatous infiltration of the bone marrow.[14] Immune-mediated thrombocytopenia occurring as a consequence of the tuberculosis infection itself is an exceedingly rare occurrence. Though usually reported in association with pulmonary TB,[6,8,15,16,] it is also documented with disseminated,[4] and lymph node TB.[3,7,9,13,17] A study from Saudi Arabia of 846 patients with tuberculosis reported that only 1% of these had ITP as the presenting feature.[21] The immune basis of tuberculosis-induced thrombocytopenia in these case reports is supported by the presence of either the platelet antigen-specific antibodies or platelet surface membrane IgG,[8,10] or by response to immunomodulatory therapy.[3,6]The pathogenesis of tuberculosis causing immune thrombocytopenia is not yet clear but has been thought to be generation of antiplatelet antibodies by lymphocytes borne as a result of clonal proliferation due to host's immune response to the tuberculous pathogen. [10]Tuberculosis infection can thus act as a trigger for ITP is susceptible individuals.

Antiplatelet antibodies were not done in our patient as she could not afford the test. However, and as highlighted in the American Society for Hematology's 1996 guidelines for the diagnosis and management of ITP[16], the absence of anti-platelet antibodies in no way invalidates the diagnosis of ITP. In fact, anti-platelet antibodies were labeled as an "unnecessary" test for the routine evaluation of patients presenting with ITP. [16]

Thrombocytopenia in tuberculosis can occur due to a defect in platelet production (marrow infiltration, fibrosis, amyloidosis),[20] as a side effect of anti-tuberculous therapy (eg: Rifampicin induced),[19] tuberculosis induced haemophagocytic syndrome, hypersplenism, tuberculosis complicated by sepsis with disseminated intravascular coagulopathy (DIC), thrombotic thrombocytopenic purpura (TTP)[20]or due to immune-mediated platelet destruction (ITP).[2-17]

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 sensitized patients.[19]Some patients may not develop thrombocytopenia for months to years. 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 an evidence of marrow infiltration with tubercular granulomas, neither was she exposed to anti-tubercular drugs prior to development of thrombocytopenia. There were no other major illness. She did not have hepatosplenomegaly to account for the peripheral platelet destruction or sequestration. Thus, the only plausible explanation is immune mediated thrombocytopenia.

The above case could be confused with coincidental presentation of ITP and tuberculosis, which are both existing as independent entities. ITP is an acquired disease of the adults. Moreover, the temporal association of the purpura with axillary lymphadenitis and normalization of platelet count with antitubercular therapy and absence of recurrence of thrombocytopenia after stopping immunomodulatory therapy further proves that tuberculosis was the cause of ITP.

All the patients cited in the literature including our case responded to immunomodulatory therapy with concomitant ATT. The fact that immunomodulatory therapy alone did not result in improvement and that effective concomitant ATT was needed as an adjunct support, establishes tuberculosis as the cause for immune thrombocytopenia.

The characteristics of reported patients with immune mediated thrombocytopenia were as follows:

1. Female,
2. Most cases were in 3rd–8th decades of life,
3. Middle-Eastern and Asian descent,
4. Most commonly associated with pulmonary tuberculosis (33%) and tubercular lymphadenitis associated in 19% of cases,
5. Initial failure to identify tuberculosis as a putative cause of thrombocytopenia.

Our case was unique in several aspects. While most of the cases reported in the world literature were middle-aged females, our patient was a young, adolescent female.

The earlier reports described mediastenal, cervical and retroperitoneal lymphadenopathy with ITP, however, our patient had axillary tubercular lymphadenopathy. In our patient, introduction of four drugs ATT led to remission of ITP within 2 weeks. Prednisolone was stopped completely. The timely recognition of tuberculosis as a cause of ITP led to the prompt treatment of thrombocytopenia.

Treatment options for tuberculosis associated ITP have been variable. Most authors have treated such cases with ATT along with steroids. Cases non responsive to steroids were treated with intravenous Ig[3,12,14], vincristine, or danazole. Others have treated with ATT alone (when platelet count is more than 20,000/cu mm) [10].

To summarize, ITP and tuberculosis are common diseases in India. A variety of hematological abnormalities occur in the context of tuberculosis. ITP is rare but potentially

treatable haematological manifestation of tuberculosis and should be considered among possible causes of thrombocytopenia in tuberculosis.

Take home message:
1. It is important we recognize and consider tuberculosis as a treatable secondary cause of immune thrombocytopenia in areas of high endemicity of tuberculosis and especially when ITP is resistant to conventional therapy.
2. As the incidence of ITP is increasing world wide, one must have a high index of suspicion for co-existing tuberculosis in non-responders, as it is responds only with the treatment of tuberculosis.[19]

CONCLUSION

This case report illustrates the causal association between immune thrombocytopenia and tuberculosis.

REFERENCES

[1] Kashyap R, Choudhary VP. Haematological manifestations of tuberculosis. In: Sharma S K and Mohan A, editors. Tuberculosis, New Delhi : Jaypee Brothers Medical Publishers; 2006. p. 370–9.
[2] P´erez de Llano LA, Soil´an del Cerro JL, Garc´ıa Pais MJ. Immue thrombocytopenic purpura as presenting form of miliary tuberculosis. Archivos de Bronconeumolog´ıa. 1998; 34: 411–2.
[3] Talbot S, Dowling A, Dowling JP, Fuller A, Schwarz M. Mediastinal nodal tuberculosis presenting as immune thrombocytopenia. Australian and New Zealand Journal of Medicine.1998;28: 465–6.
[4] Hernandez-Maraver D, Pelaez J, Pinilla J, Navarro FH. Immune thrombocytopenic purpura due to disseminated tuberculosis. Acta Haematol. 1996;96: 266 – 8.
[5] Al-Majed SA, Al-Momen AK, Al-Kassimi FA, Al-Zeer A, Kambal AM, Baaqil H. Tuberculosis presenting as immune thrombocytopenic purpura. Acta Haematol. 1995;94: 135–8.
[6] Yasuda Y, Matsubara Y, Watanabe S, Hatakenaka R, Funatsu T, Ikeda S. A case of intractable pulmonary tuberculosis complicated by idiopathic thrombocytopenic purpura (ITP). Nippon Kyobu Geka Gakkai Zasshi. 1994;42: 2301–5.
[7] Pavithran K, Vijayalekshmi N. Thrombocytopenic purpura with tuberculous adenitis. Indian Journal of Medical Sciences. 1993;47: 239–40.
[8] Boots RJ, Roberts AW, McEvoy D. Immune thrombocytopenia complicating pulmonary tuberculosis: case report and investigation of mechanisms.Thorax. 1992;47: 396–7.
[9] Singh SP, Misra GC, Prusty PK, Das RK. Tubercular lymphadenitis with purpura. Journal of the Indian Medical Association.1986;84: 247–9.
[10] Jurak SS, Aster R, Sawaf H.Immune thrombocytopenia associated with tuberculosis. Clinical Pediatrics.1983;22: 318–9.

[11]Chia YC, Machin SJ. Tuberculosis and severe thrombocytopaenia. British Journal of Clinical Practice.1979;33: 55–8.
[12] Cockcroft DW, Donevan RE, Copland GM, Ibbott JW. Miliary tuberculosis presenting with hyponatremia and thrombocytopenia. Canadian Medical Association Journal. 1976;115: 871–3.
[13] Levy M, Cooper BA.Thrombocytopenic purpura associated with tuberculous lymphadenitis. Canadian Medical Association Journal. 1964;90: 373–4.
[14] Ghobrial MW, Albornoz MA. Immune thrombocytopenia: A rare presenting manifestation of tuberculosis. American Journal of Hematology. 2001;67: 139–43.
[15] Akyildiz B, Uzel N, Yanni D, Itak AC, Karab M¨oc¨uo˘glu, ¨ Uc¸sel R. Immune thrombocytopenic purpura associated with pulmonary tuberculosis.Turkish Journal of Pediatrics. 2009;51: 271–4.
[16] Ursavas A, Ediger D, Ali R, Köprücüoglu D, Bahçetepe D, Kocamaz G. Immune thrombocytopenia associated with pulmonary tuberculosis. Journal of Infection and Chemotherapy. 2010;16: 42–44.
[17] Surana AP, Shelgikar MK, Melinkeri S, Phadke A. Immune thrombocytopenia (ITP): A Rare Association of Lymphnode Tuberculosis. Journal of the assoc. of physicians of India. 2014;62: 74-76.
[18] Glasser RM, Walker RI, Herion JC. The significance of hematologic abnormalities in patients with tuberculosis. Arch Intern Med. 1970;125:691-5.
[19] Mehta YS, Jijina FF, Badakere SS, et al. Rifampicin-induced immune thrombocytopenia.
Tuber Lung Dis. 1996;77: 558.
[20] Tapan Das B, Sibes Kumar D, Pulak Kumar J, Somnath B. Immune Thrombocytopenic Purpura Associated with Pulmonary Tuberculosis. J Glob Infect Dis. Department of Tuberculosis and Respiratory diseases, North Bengal Medical College, Sushratanagar, Darjeeling, India1Department of Tuberculosis and Respiratory diseases, Medical College, Kolkata, India2012;4: 175–177.