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Case Report

Autoimmune Hemolytic Anemia and Thrombocytopenia with Tuberculous Lymphadenitis: A Case Report and Review of Literature

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ABSTRACT

Tuberculosis (T.B) is a major burden in developing countries and it is re-emerging in developed countries. It is global cause of morbidity and mortality. Tuberculosis is associated with a number of hematological manifestations with anemia of chronic disease being the most common. A few cases of Autoimmune Hemolytic Anemia associated with tuberculosis are reported in the literature amongst which only three were in children. Amongst these bicytopenia (anemia and thrombocytopenia) was reported in only one case. Here, we report a case of Autoimmune Hemolytic Anemia and thrombocytopenia with tubercular lymphadenitis leading to extravascular hemolysis in a six-year-old female child. To our best knowledge, it is the youngest patient to present with this entity.

Keywords: Autoimmune hemolytic anemia; Thrombocytopenia; Tuberculosis; Child

INTRODUCTION

Tubercular infection has a diverse spectrum of manifestations involving various organs. Amongst the hematological manifestations anemia of chronic disease is the most common. Autoimmune hemolytic anemia in tuberculosis is quite rare with an incidence of 1-3 cases per 100,000 population per year [1]. Altered immune response is believed to be the cause of hemolysis but the pathogenesis is not clear [2]. Also, presence of thrombocytopenia along with anemia makes it further rare entity. Most of the reported cases of autoimmune hemolytic anemias are in adults with a very few cases in children.

CASE REPORT

A six years old female child presented with high grade fever which was not associated with chills and was more frequent during evening time, yellowish discoloration of skin and sclera, and loss of weight and appetite for last three months. She had no previous history or family history of hemolytic anemia. Also, there was no history of any drug intake. On general physical examination patient was febrile, pallor and icterus were present.

Her heart rate was 110/min and respiratory rate was 25/min. She had a single right cervical lymph node palpable measuring 1 × 0.5 cm^2, firm in consistency, mobile and nontender. On abdominal palpation both liver (two fingers below costal margin) and spleen (three fingers below costal margin) were enlarged (Table 1).

A complete blood count and peripheral smear was done which showed anemia with hemoglobin of 6 gm/dl, total leucocyte count (7600/mm^3) was normal and platelets (34,400/mm^3) were decreased. On peripheral smear examination red blood cells (RBCs) showed moderate anis poikilocytosis with predominantly normocytic normochromic picture with presence of polychromatic cells, spherocytes and nucleated RBCs. Reticulocyte count was raised (6.4%). Biochemical parameters were as follows: total bilirubin was raised (1.4 mg/dl), indirect bilirubin was (1.0 mg/dl).

Serum urea and creatinine were within normal limits. Serum haptoglobin was slightly reduced 0.12 g/l (normal range 0.16-2 g/l) Serum lactate dehydrogenase was markedly raised (1123 IU/ml). Direct coombs test was positive (3+) for IgG and C3d. Tests for hepatitis B, hepatitis C, human immunodeficiency virus, mycoplasma, enteric fever, malarial parasite was negative. Anti dsDNA antibodies were negative.

Fine needle aspiration cytology (FNAC) of the cervical lymph node was performed which revealed granulomatous lymphadenitis, however acid-fast bacilli was not demonstrated. Based on all these clinical and laboratory finding a diagnosis of

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autoimmune hemolytic anemia and thrombocytopenia with warm autoantibodies was established.

Table 1: Laboratory parameters of the patient during her stay in hospital.

Parameter	Day 0	Day 5*	Day 10**	Day 15***	Day 40
Hemoglobin (g/dl)	6	7	9.6	10.3	11
TLC (cells/mm^3)	7600	8180	9220	7040	16400
Platelets (cells/mm^3)	34400	79000	487000	492000	483000
Spherocytes on P. S	++	+	++	Occasional	Absent
Polychromatic cells on P. S	+	+	Absent	Absent	Absent
nRBCs/100 WBC on P. S	+	+	Absent	Absent	Absent
Retic count	6.40%	3.80%	2.60%	2.10%	2.20%
LDH	1122	-	-	-	150
Total bilirubin	1.4	-	-	-	1
Indirect bilirubin	1	-	-	-	0.2
Cervical LN size (cm^2)	1 × 0.5	-	2 × 2.5	3 × 3	1.5 × 1
Splenomegaly	Palpable	-	-	-	Nonpalpable

Note: *After five days of glucocorticoids administration, **Post transfusion of two packed red blood cells, ***Antitubercular drugs started.

The patient was started on glucocorticoids and two units of packed cells were transfused. With the administration of steroids, the hematological parameters came towards normal range. But over next week she started having more frequent episodes of fever and her cervical swelling increased in size from 1 × 0.5 cm^2 to 3 × 3 cm^2. A repeat FNAC was done which yielded frank pus. Smears prepared show necrotic granular material and Ziel Nelson stain for AFB was found to be positive. Thus, a diagnosing of AIHA with thrombocytopenia (Evans syndrome) associated with tuberculosis was given.

The patient was started on Antitubercular (ATT) drugs and steroids were tapered and then stopped over next week. The patient responded to ATT. Her cervical swelling started to decrease, and her hematological parameters came within normal limits with no evidence of hemolysis over a few weeks.

Table 2: Review of literature with case reports of tuberculosis associated autoimmune hemolytic anemia.

Study authors	Age (years)/sex	Presentation	Type of antibody	Management
Cameron	58 /M	Pulmonary	Cold	ATT, PC, St.
Semchyshyn	39/F	Genitourinary	Cold	ATT, St.
Murray	49/M	Pulmonary	Warm	ATT
Siribaddana	37/M	Lymph Node	Cold	ATT
Blanche	42/M	Disseminated	Warm+Cold	ATT, PC, St., Sx
kua	26/M	Disseminated	Warm	ATT
Turgut	30/F	Pulmonary	-	ATT

Abba	21/F	Gastrointestinal	Warm+Cold	ATT, PC
Bakshi*	8/F	Disseminated	Warm+Cold	ATT, PC, St.
Gupta*	8/M	Abdominal	-	ATT, St.
Khemiri	11/F	Pulmonary	Warm	ATT
Nandennavar	19/F	Lymph node	-	ATT
Wu	24/F	Disseminated	Cold	ATT, PC
Somalwar*	22/M	Disseminated	-	ATT, PC, St.
Kumar*	23/M	Pulmonary	-	ATT
Safe	18/F	Pulmonary	Warm	ATT, PC
Bahbahani	24/F	Lymph node	Warm	ATT, PC, St.
Anurag*	25/F	Pulmonary	Cold	ATT, Pc
Shamshad GU	68/F	Pulmonary	Cold	ATT

Note: M: Male; F: Female; ATT: Antitubercular Treatment; PC: Packed Cell; St.: Steroids; Sx: Surgery (splenectomy), *Cases reported from India [2,6-22].

DISCUSSION

Autoimmune Hemolytic Anemia (AIHA) is of two types: idiopathic (primary) and secondary. Secondary AIHA is associated with infections, lymphoproliferative disorders, connective tissue disorders or drugs. Infections commonly associated with AIHA are Mycoplasma, Epstein Barr virus, cytomegalovirus, HIV, mumps, measles, rubella, visceral leishmaniasis and few acute bacterial infections [3,4]. AIHA is associated with warm or cold auto antibodies which are formed against red cell membrane self-antigens. They lead to antigen antibody reaction and lysis of RBCs. Hematological abnormalities are commonly associated with tuberculosis which can be due to malabsorption, nutritional insufficiency, shortened life span of red blood cells (RBCs), disruption in iron utilization and/or bone marrow infiltration. However, AIHA associated with tuberculosis is rare with 20 cases reported in the English literature [5]. The first case was reported in 1974 by Cameron SJ in a 58 years old male who had pulmonary tuberculosis with AIHA. Most of the reported cases reported are from India reflecting the high prevalence of the disease. Till date, only 3 pediatric cases have been reported with this entity with thrombocytopenia in only one case amongst which the present case is of youngest age (Table 2) [2,6-22].

The autoantibodies against the RBC antigens can be warm, cold or mixed based on their ability of binding to RBCs and causing hemolysis. Cold autoantibodies which are mostly Ig M type cause complement fixation and agglutinate the RBCs. These are active in temperature 28-31°C or even up to 37°C and cause intravascular hemolysis. Whereas warm autoantibodies are usually Ig G type and are responsible for splenic removal of sensitized RBCs leading to anemia. These may or may not be responsible for complement fixation [6]. These may or may not be responsible for complement fixation. The lysis of RBCs can be either complement mediated or by optimization of RBCs by immunoglobulins followed by phagocytosis or both. The present case had warm autoantibodies with direct coombs test positive for IgG and C3d leading to extravascular hemolysis (Figure 1).

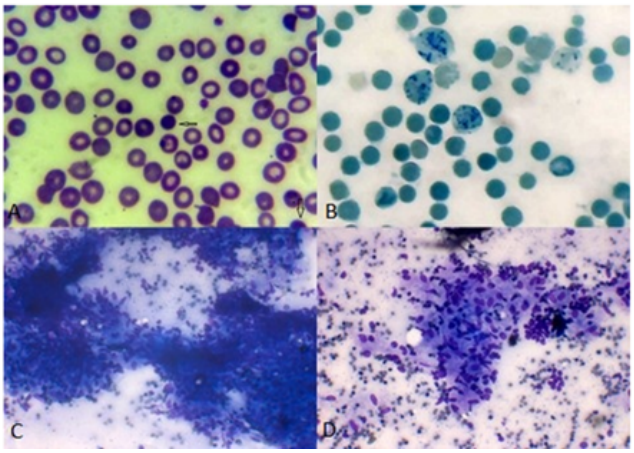

Figure 1: (A) Peripheral smear showing spherocytes, arrow marked (Giemsa, oil immersion), (B) New methylene blue stain- increased reticulocyte count (oil immersion) Fine needle aspiration cytology of lymph node (Giemsan stain) showing, (C) granulomatous lymphadenitis (200X), (D) epithelioid cell granuloma (400X).

Thrombocytopenia in the present case was also believed to be due to tuberculosis, as it improved only with treatment of tuberculosis. Immune thrombocytopenia associated with tuberculosis was also reported by khemiri et al [7] in pediatric patients (Figure 2).

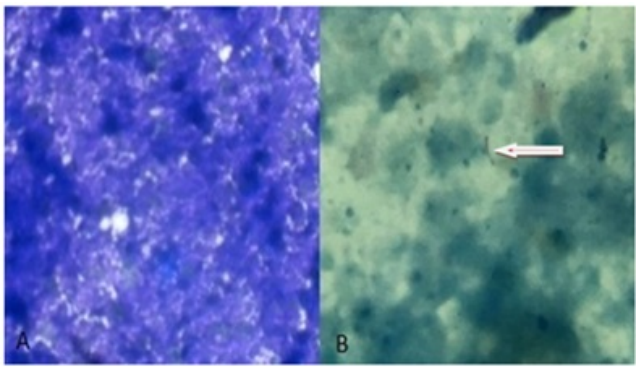

Figure 2: (A) FNAC lymph node post steroid showing necrosis (Giemsa, 200X), (B) Acid fast bacilli positive, arrow mark (Zeil Nelson stain, oil immersion).

The search of underlying cause is very important which can be often challenging as with the present case. Inadvertent treatment of AIHA and thrombocytopenia with steroids can lead to serious consequences and flare up of tubercular infection if undiagnosed. The present patient also had dramatic increase in cervical lymph node on administration of glucocorticoids for AIHA. These patients generally respond to ATT alone as seen with our patient. Blood transfusion is done if severe anemia is present. She had good response to ATT with control of hemolysis and normal platelet count. A good response to ATT is the indicator that the underlying cause of hemolysis and thrombocytopenia was tuberculosis [7,8].

CONCLUSION

Although tuberculosis is a rare cause of AIHA and thrombocytopenia, it should be kept in differential diagnosis in countries like India where a high burden of the disease is present. The treatment of AIHA and thrombocytopenia associated with tuberculosis with steroids alone can produce serious complications thus, early administration of ATT or ATT with steroids if AIHA /thrombocytopenia is not responding to ATT alone is required in these cases.

CONFLICTS OF INTEREST

None.

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