Case Report

Pancytopenia without Hepatosplenomegaly: A Rare Manifestation of Extrapulmonary Tuberculosis in an Adolescent Boy

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Abstract

Extrapulmonary tuberculosis (TB) is a well-recognized cause of pyrexia of unknown origin. However, clinical presentation of TB in children with isolated hematological abnormalities is extremely rare. Anemia, usually normocytic, normochromic, leukopenia, leukocytosis, thrombocytopenia, thrombocytosis, and monocytosis are more common complications of TB rather than pancytopenia. Only anecdotal case reports and small case series are available in this regard. We are reporting an 18-year-old boy who presented with on and off low-grade fever for 3 months and anorexia and progressive pallor for 1 month. After extensive workup, pancytopenia remained unexplained. Bone marrow (BM) examination revealed caseating granulomas, along with Mantoux positivity and contact with sputum-positive pulmonary TB. He responded favorably to antitubercular therapy (ATT) within 2 months. This report alerts clinicians to be vigilant regarding the rare possibility of BM TB while investigating unexplained pancytopenia, as it is completely reversible with ATT.

Keywords: *Bone marrow cells, tuberculosis, pulmonary, pancytopenia*

Introduction

Extrapulmonary tuberculosis (EP-TB) is a well-recognized cause of pyrexia of unknown origin.[1,2] Risk of lympho-hematogenous spread is higher in young children, making them more vulnerable for EP-TB. In children, often the symptoms and signs of EP-TB are nonspecific and isolation of tubercular bacilli is difficult due to paucibacillary disease lowering the sensitivity of diagnostic tests, but delay in initiating antitubercular therapy (ATT) can lead to morbidity and mortality.[2] Thus, it is recommended to initiate ATT empirically early in suspected EP-TB cases, when clinical and/or radiologic findings are compatible, and the symptoms cannot be explained by any other definitive etiology, even when it is not possible to isolate the tubercular bacilli by acid-fast bacilli (AFB) staining or nucleic acid amplification test.[2]

Lymph node, gastrointestinal system, central nervous system, and osteoarticular system are commonly affected by EP-TB.[2] However, the clinical presentation of TB in children with isolated hematological abnormalities is extremely rare.[1] Anemia, usually normocytic, normochromic, leukopenia, leukocytosis, thrombocytopenia, thrombocytosis, and monocytosis are more common complications of TB rather than pancytopenia.[1] Only anecdotal case reports and small case series are available in this regard.[1-4] Informed consent from the father of the patient was taken, and clearance from the institute ethics committee was also obtained before publishing the case.

Case Report

An 18-year-old boy presented with on and off low-grade fever for 3 months and anorexia and progressive pallor for 1 month. The fever was more in evening times as remembered by the caregivers but was not associated with chills/rigor. There were no symptoms suggestive of respiratory, cardiovascular, gastrointestinal, hepatic, or renal involvement such as cough, fast breathing, breathlessness, pain abdomen, abdominal distension, jaundice, and change in color or amount of urine output. There was no history of any drug ingestion, apart from paracetamol during these 3 months and before that. Apart from pallor, the systemic examination was otherwise normal.

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Hematological parameters revealed hemoglobin of 6 g/dl, normocytic and normochromic red blood cells, leukocyte count of 2640/µl, 64% lymphocytes, platelet count of 37,500/µl, and erythrocyte sedimentation rate was 22 mm in 1st h. Peripheral smear did not show any hemoparasites or any other abnormalities. Liver and kidney function tests, autoimmune profile, serum triglyceride, and ferritin levels for hemophagocytic lymphohistiocytosis (HLH), workup for viral and parasitic causes including malaria, hepatitis B and C, Epstein–Barr virus, parvovirus, and human immunodeficiency virus (HIV) were noncontributory. Workup for atypical bacterial infections such as bartonellosis and brucellosis was also negative. Serum Vitamin B12, folate, and lactate dehydrogenase levels were normal. Although Mantoux test showed an induration of 11 mm at 48 h, Chest X-ray was normal, and ultrasound abdomen showed only a few subcentimeteric mesenteric lymph nodes. Computed tomography of neck, chest, and abdomen also did not reveal any significant abnormality.

On asking leading questions, the parents revealed paternal grandfather is taking ATT for sputum-positive pulmonary TB for the past 5 months. Subsequently, bone marrow (BM) examination was performed, which revealed a hypocellular marrow, no blast cells, with infiltration by epithelioid granulomas having central caseating necrosis. Stain for AFB and GeneXpert was negative, but in view of positive contact history and corroborative findings, the diagnosis of bone marrow TB was considered. Sarcoidosis was ruled out as serum angiotensin-converting enzyme level, and urine calcium creatinine ratio was normal. He showed favorable clinical response with slow improvement in hematological parameters (repeat Hb-9 g/dl, total leukocyte count – 5670/µl, platelet count – 152,000/µl) and resolution of pyrexia within 2 months after starting ATT. Currently, on follow up after 1 year of instituting ATT, the child has completed the course of ATT 6 months back, latest hematological parameters are all within normal limits.

Discussion

This report alerts clinicians to be vigilant regarding the rare possibility of BM TB while investigating unexplained pancytopenia, as it is completely reversible with ATT. Isolation of tubercular bacilli by acid-fast staining or nucleic acid amplification tests such as GeneXpert, although difficult needs to be attempted in such cases. However, ATT may be started without demonstrating AFB as previously mentioned, when corroborative evidence such as caseating epithelioid granulomas and Mantoux positivity are available. TB is the most predominant causes of BM granulomas (48% of cases). Noncaseating granuloma remains the most common finding (33%–100%), while caseating granulomas are uncommon (29%).[5,6]

Etiopathogenesis behind pancytopenia in TB includes hypersplenism, maturational arrest, histiocytic hyperplasia, or infiltration of BM by caseating/noncaseating epithelioid granulomas often leading to fibrosis in BM.[3] HLH may rarely occur after TB and can cause pancytopenia and splenomegaly.[4] BM infiltration by granulomas may present without hepatosplenomegaly rarely. Dalugama and Gawarammana also reported a 56-year-old male with BM TB, who presented with fever and pancytopenia and only had mild hepatosplenomegaly.[7] In a large adult case series of 22 BM TB cases, all cases had involvement of other sites and ten cases (45%) died within 2 weeks. Nine patients had other comorbidities such as HIV infection, solid organ transplantation, and diabetes.[8]

Yadav *et al*. have also described a 5-year-old boy, who presented with pyrexia and pancytopenia with granulomas in BM and later responded to ATT, and in this case also, the decision for starting ATT was based on corroborative evidence only. Tubercular granulomas not only infiltrate and replace the marrow cells but also cause BM suppression through release of interferon and lymphotoxin.

As such, only about 0.38% of TB patients show evidence of BM granulomas.[4] However, surprisingly, granulomas in BM in children with disseminated TB can be detected in a proportion of cases. Nevertheless, pancytopenia as a presenting symptom is extremely rare in these cases despite the presence of tuberculous granulomas in BM.

Children with miliary TB, pancytopenia, and caseating granulomas in the BM often have a poor prognosis and high mortality, whereas those with noncaseating granulomas have been shown to have a better chance of survival. Although the precise reason behind this variable outcome is unknown, Yadav *et al*. attributed this to the immunity of the host, virulence of the bacteria, and delay in initiation of appropriate treatment. Other causes of noncaseating granulomas with pancytopenia in BM including leprosy, syphilis, brucellosis, and sarcoidosis were ruled out in our case by appropriate clinical and laboratory examination, and this is required in all such cases before initiating ATT.[9]

Overall, BM TB has poor outcome as compared to pulmonary TB, with mortality as high as 50%.[5] Associated immunocompromised state, opportunistic infections, delay in diagnosis, and initiation of appropriate treatments are possible explanations for such poor outcomes.[6]

Conclusion

In cases with unexplained isolated pancytopenia, BM biopsy needs to be screened for TB, even in the absence of suggestive history and ancillary investigations.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's parents have given their child consent for their child's images and other clinical information to be reported in the journal. The patient's parents understand that their child's name

and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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