Disseminated Tuberculosis: Interesting Hematological Observations

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Abstract
Disseminated tuberculosis can present in various ways including prolonged fever / pyrexia of unknown origin, hepatosplenomegaly, lymphadenopathy, meningitis and rarely extreme forms of hematological abnormalities such as pancytopenia and leukemoid reaction. We hereby report a case who presented with short history of fever, associated with vomiting and altered sensorium. He also had evidence of meningitis on neuroimaging with equivocal CSF finding. During his stay, he showed a spectrum of interesting hematological findings, including severe pancytopenia on peripheral smear, hemophagocytosis, epithelioid cell granuloma with Langhans’ giant cells and focal necrosis consistent with tuberculosis on bone marrow examination. He showed an excellent clinical as well as hematological response to four drug antitubercular treatment (RHZE). The report highlights the significance of hematological picture in final confirmation of tuberculosis which may otherwise be passed off as nutritional or other unrelated causes.

Introduction
Disseminated tuberculosis can present with various clinical features. When associated with pulmonary lesion, diagnosis is quite easy. In absence of pulmonary lesion especially in presence of hematological findings, a number of differential diagnoses are likely unless a confirmation is possible on bone marrow examination. Hematological manifestations can vary from anemia of different types, pancytopenia, leucoerythroblastic anemia, leukemoid reaction, rarely dissemination intravascular coagulation (DIC) and even myelofibrosis. We describe below a patient who presented as meningitis and during his stay showed a myriad of hematological findings including bone marrow tuberculosis and finally an excellent response to anti-tubercular treatment.

Case Report
A 22 years old male was admitted with moderate to high grade fever associated with vomiting for 4 days and history of altered sensorium on the day of admission. There was no history of seizure, tuberculosis in past and patient’s attendant also denied any history of contact with tuberculosis. On examination his vitals were stable. He had altered sensorium, bilateral pupils were dilated and sluggishly reacting, bilateral plantars were equivocal and signs of meningeal irritation were present. Fundoscopy showed bilateral incipient papilloedema and non-contrast computed tomography head showed prominence of ventricular system. X-ray chest and ultrasound abdomen were normal. Clinical diagnosis of pyogenic meningitis was made and he was started on IV antibiotics, mannitol and steroid. Investigations revealed hemoglobin of 11.2 g/dl, total leucocyte count (TLC) 11500/mm³, platelet count was 36,000 and reticulocyte count <1%. Peripheral smear showed red cells with mild anisocytosis, predominant normochromic with few microcytic hypochromic cells, leucopenia with absolute neutropenia and thrombocytopenia. Considering pancytopenia bone marrow aspiration was done which showed scant scattered mainly mononuclear cells with marked nuclei, mature lymphocytes and occasional plasma cells. There was hemophagocytosis of megakaryocytes along with some platelets. Myeloid precursor and mature cells were conspicuously depressed. In view of large number of hemophagocytic cells, possibility of hemophagocytic syndrome secondary to infection / hypoplastic marrow / any hematopoietic malignancy was suggested and bone marrow biopsy was done, which revealed epithelioid cell granuloma with Langhans’ giant cells and focal necrosis consistent with tuberculosis. He was put on four drug antitubercular treatment, steroid, phenytoin, along with IV fluids and two units of whole blood were also transfused. Patient showed gradual improvement in hematological as well as in clinical profile and became normal after 4 weeks of therapy.

Discussion
This patient is interesting because of an acute presentation of tubercular meningitis based on definitive evidence on imaging and equivocal CSF findings, but diagnosed on the basis of associated findings on bone marrow biopsy. Patient also demonstrated pancytopenia, hemophagocytic syndrome...
on bone marrow smear and finally demonstration of granuloma and necrosis on bone marrow biopsy specimen. Patient showed remarkable recovery to antitubercular treatment with reversal of hematological abnormalities.

Mild leucocytosis has been uniformly found in 6-16% of patients especially in miliary tuberculosis and there may be “shift to left” with increased premature forms in the peripheral blood. Pancytopenia as seen in our patient developing about two weeks after initial leucocytosis is an uncommon hematological manifestation seen in about 8% cases and may rarely result in bleeding diathesis also. Numerous hypotheses have been put forward to explain the occurrence of pancytopenia in disseminated tuberculosis, such as hypersplenism, histiocytic hyperplasia and phagocytosis, bone marrow infiltration by tubercular granuloma or occasionally maturation arrest. Histopathological changes in the bone marrow can range from normal marrow to typical granuloma formation, marrow hypoplasia and necrosis of the marrow. Normal to increased cellularity is commonly found in two-third of the patients and rarely leukemoid reaction in the peripheral blood along with increased myelopoiesis may be seen.

Haemophagocytic syndrome is a rare but potentially life threatening condition, characterized by anemia (100%), neutropenia (65%), thrombocytopenia (91%), pancytopenia (74%) and morphological evidence of macrophage phagocytosis of red cells, granulocytes and platelets. The marrow can be hypocellular in about one-third of the patients with hemophagocytosis syndrome as seen in our case. This syndrome has been associated with immune deficiency, lymphoma, viral infection, fungal, bacterial as well as in parasitic infection. In such circumstances, a bone marrow biopsy becomes essential to exclude a possibility of aplastic anemia or some infiltration. In the present case, definitive diagnosis of tuberculosis could be achieved by demonstrating epithelioid cell granuloma Langhans’ giant cells and focal necrosis in bone marrow biopsy specimen only. Severe but potentially reversible hemophagocytosis has been associated with certain infections like babesiosis, HIV and occasionally with SLE and Still’s disease etc.

References