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Case Report

Extra pulmonary tuberculosis presenting as fever with massive splenomegaly and pancytopenia

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ABSTRACT

Disseminated tuberculosis is an important differential diagnosis for fever of unknown origin (FUO) and it can present with hepatosplenomegaly and lymphadenopathy and may have meningitis and with hematological abnormalities including pancytopenia or a leukemoid reaction. We report the case of a 13-year old male who presented with fever, weight loss, pallor and massive splenomegaly with pancytopenia, in whom a bone marrow trephine biopsy showed caseating granulomata, who responded well to antituberculous treatment and has remained healthy on follow up after nine years.

Introduction

Tuberculosis is one of the most common and well-described infectious diseases, with a worldwide distribution and a vast spectrum of clinical manifestations. We report a case of extra-pulmonary tuberculosis presenting as fever with massive splenomegaly and pancytopenia. Recognition of pancytopenia due to bone marrow infiltration by *Mycobacterium tuberculosis* is important as the infection is curable if timely recognized since a delay in diagnosis may result in fatal outcome.

Case report

A 13-year old male, a native of Kerala, India, a student was referred in January 2006 for high grade intermittent fever with rigors and chills of one month duration. He did not complain of cough, hemoptysis, neck swellings or other associated symptoms. He had not traveled outside his district. The young man reported a history of bronchial asthma for last 10 years requiring very occasional treatment with bronchodilators. He did not use alcohol or tobacco. No significant family history except that his father having diabetes. His parents noticed significant weight loss and loss of appetite. On physical examination he was moderately built, anicteric and poorly nourished with pallor with pulse: 108/mt. and temp. 101 °F. There was no lymphadenopathy, bleeding manifestations, rash or eschar. Abdominal examination revealed a firm non-nodular liver 5 cm below the right costal margin and an enlarged spleen of 10 cm below the left costal margin (Fig. 1). No ascites was noted. Optic fundi examination was normal.

Investigations

His CBC on admission (01/29/06) was showed a leukocyte count of 1000/mm^3, platelet count 17,000/mm^3 and Hb 7.7 g/dL. Repeated on 02/05/06, the CBC revealed leukocyte count of 500, platelet count 25,000 and Hb 6.2. Urine analysis was normal. Liver function tests showed normal ALT (33 IU/L) and total bilirubin (0.2 mg/dL) with low albumin (2.5 g/dL), total protein (5.8 g/dL) and mildly elevated alkaline phosphatase (240 IU/L). A tuberculin skin test was negative. HIV ELISA, hepatitis B surface antigen, monospot and ANA were all negative. A chest X-ray was unremarkable. An abdominal ultrasound confirmed hepatosplenomegaly and also found enlarged paraaortic lymph nodes and ascites which were felt to be suggestive of lymphoma. A bone marrow aspiration was interpreted as showing maturation arrest and a bone marrow trephine biopsy was done.

Abbreviations: ESR, erythrocyte sedimentation rate; FUO, fever of unknown origin.

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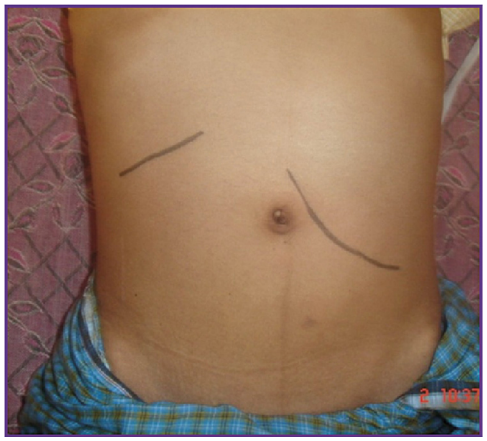

Fig. 1. Abdomen showing hepatosplenomegaly.

The patient's overall clinical status worsened. He continued to be febrile, and developed epistaxis, and purpurae as well as enlargement of several cervical lymph nodes. He was supported with packed RBC and platelet rich plasma. Urine and blood cultures for common bacteria were negative and echocardiogram was unremarkable. High temperature spikes of 101–105 °F, weight loss and mucosal bleeds persisted. At that point, his bone marrow trephine biopsy pathology was reported to show the presence of epithelioid cell granulomata with Langhans giant cells and focal necrosis consistent with tuberculosis (Fig. 2). AFB stain was negative.

Antituberculous treatment (ATT) with a combination of isoniazid, rifampin, ethambutol pyrazinamide was initiated. The patient developed an urticarial rash with wheezing. Suspecting hypersensitivity, his ATT was changed to ofloxacin, ethambutol and streptomycin for one month and then switched back to the original therapy which he then tolerated without incident. The young man became afebrile after 3 weeks and his blood counts slowly improved. He was continued on the 4 drug ATT for 2 months after restarting and then switched to the combination of isoniazid and rifampin for 10 additional months. Follow up laboratory results are given in Table 1.

On follow up after 6 months, he was afebrile and had normal growth milestones. His abdominal ultrasound examination documented decreasing size of his liver and spleen. The final diagnosis of extrapulmonary tuberculosis with hepatosplenomegaly and bone marrow infiltration with pancytopenia was made. In 2015, nine years after presentation of his illness, he remained healthy, asymptomatic and weighing 64 kg.

Discussion

Tuberculosis continues to be a major public health problem in India. It is an important cause of fever of unknown origin with nonspecific signs and symptoms making an early diagnosis difficult. Disseminated disease without the characteristic miliary pattern on chest radiograph or extrapulmonary disease without clear localizing features is the most frequent presentations [1]. Varying hematological manifestations associated with disseminated tuberculosis have long been recognized [2]. Our patient presented with fever and chills of more than two months duration with pancytopenia complicated by purpurae and mucosal hemorrhages.

In most causes of FUOs, relatively normal ESR results may exclude a serious underlying disease [3], but in our patient all values ESR values were 55 mm/h or less.

Tuberculosis may rarely present with pancytopenia and the recovery of peripheral blood counts with antituberculous therapy is taken to indicate that there is no underlying hematological disease. Several factors are considered to cause pancytopenia in disseminated or extrapulmonary tuberculosis including hypersplenism, histiocytic hyperplasia, maturation arrest, or infiltration of the bone marrow by caseating or noncaseating granulomas causing reversible or irreversible fibrosis [4]. One study of hematological manifestations of tuberculosis [5] reported that normocytic normochromic anemia was the most common abnormality observed. Other hematological abnormalities of the white blood cells include leukopenia, neutropenia, lymphocytopenia, monocytopenia, leukocytosis, neutrophilia, lymphocytosis and monocytosis. Pancytopenia was observed only in patients with disseminated/miliary tuberculosis. Thrombocytopenia was more

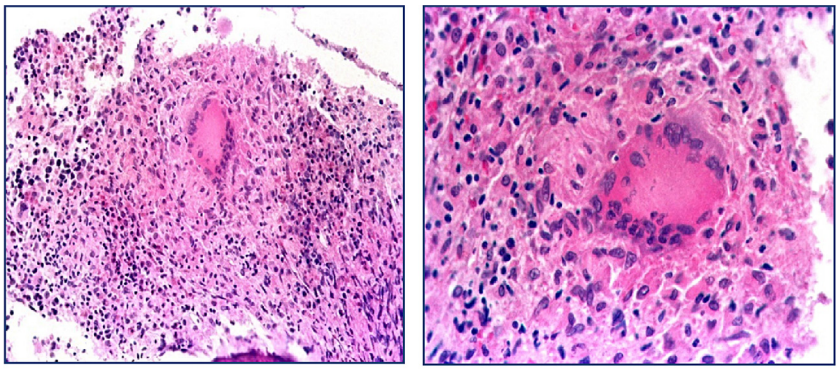

Fig. 2. Bone marrow trephine: epithelioid granuloma with Langhans giant cells.

Table 1
CBC results.

Normal range	01.29.06	02.05.06	02.21.06	12.09.06	02.03.07	10.07.11
Hgb (12–16 g/dL)	7.7	6.2	7.3	13.5	12.5	14.1
WBC (4000–11,000/cu mm)	1000	500	800	3500	4700	4400
Platelet (144,000–440,000/cu mm)	17,000	25,000	11,000	95,000	116,000	144,000
ESR (0–5 mm/1st hr)	37	24	55	15	48	10
Body weight (kg)	39	–	40	–	51	61

common in patients with disseminated/miliary tuberculosis. The patients of disseminated/miliary tuberculosis with granulomas in the bone marrow had certain significant differences as compared to patients without granulomas. These patients showed severe anemia, peripheral monocytopenia and bone marrow histiomonocytosis. The CBC reverted to normal with antituberculous therapy in these patients [5].

Bone marrow biopsy may demonstrate granulomata in one half of cases, but the yield is greater than 80% when anemia, leukopenia, and monocytosis are present [1]. The incidence of bone marrow granuloma ranges from 0.38% to 2.2% in different reports in bone marrow biopsy series [5,6]. In the series of 0.38%, 65% were diagnosed with tuberculosis [6].

Tuberculosis is not generally included as a cause of a massively enlarged spleen which usually include chronic myeloid leukemia, myelofibrosis, Gaucher's disease, lymphoma, hairy cell leukemia, Kala-Azar, tropical splenomegaly syndrome, and thalassemia. Evans and colleagues however reported a 29-year-old Caucasian woman with massive hepatosplenomegaly, jaundice and pancytopenia in miliary tuberculosis who responded to treatment [7].

Conclusions

We report a case of fever, weight loss and splenomegaly presenting with pancytopenia. Diagnosis came from bone marrow trephine biopsy. The patient had a stormy hospital course but responded to ATT with regression of splenic size and the blood picture reverted to normal and remains healthy with a nine year follow up. Early diagnosis and prompt initiation of treatment is crucial for a favorable outcome in these patients.

Conflict of interest statement

The authors declare that they have no competing interests.

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None.

Patient's consent

Informed consent was obtained from the patient for publication of this case report and accompanying images.

Authors' contributions

Dr. R. Chandni and Dr. V. Udayabhaskaran were involved in patient care and carried out the clinical assessment; Dr. R. Chandni collected data, reviewed the literature and drafted the manuscript. Dr. V. Udayabhaskaran critically revised it. Dr. G. Rajan participated in carrying out the diagnostic procedures and writing the manuscript. All authors read and approved the final manuscript.

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