Tuberculosis of the Spleen as a Cause of Fever of Unknown Origin and Splenomegaly

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Background/Aims: Splenic involvement of tuberculosis, which is rare, warrants better definition in the current era of resurgence of tuberculosis. **Methods:** Out of 339 splenectomies performed between January 1989 and December 2008 for indications other than trauma, histopathologic analysis of the spleen revealed tuberculosis in 8 patients. **Results:** All eight patients were referred for splenectomy due to fever of unknown origin (FUO). No patient was infected with HIV, and all had at least moderate splenomegaly and hepatomegaly. Three patients had hypersplenism with bleeding manifestations. Radiologic evaluations demonstrated that splenic lesions were present in five patients. Five patients had evidence of tuberculosis manifested as enlarged splenic hilar lymph nodes, cystic lymph nodes, or liver. Two patients exhibited tubercle bacilli in their sputum during the post-operative period. **Conclusions:** In areas where tuberculosis is prevalent, tuberculosis should be considered in the differential diagnosis of patients presenting with FUO and splenomegaly. Extrasplenic involvement is usually seen in splenic tuberculosis, although it may not be apparent at presentation. Splenic tuberculosis can present in isolation without extrasplenic involvement, and even in immunocompetent individuals. (*Gut Liver* 2010;4:94-97)

Key Words: Splenic tuberculosis; Fever of unknown origin; Splenomegaly

INTRODUCTION

Extrapulmonary tuberculosis is increasingly reported world wide because of the HIV epidemic. Splenic tuber-

culosis is a rare form of abdominal tuberculosis. It is usually seen in immunocompromised individuals or as a part of disseminated tuberculosis^{1,2} although it can also be manifested in immunocompetent individuals infrequently.^{3,4} Spleen can be the only site of tuberculous infection (isolated splenic tuberculosis).^{5,6} Majority of the information regarding splenic tuberculosis are in the form of case reports. Better definition of this disease will be required in this era of resurgence of tuberculosis. Here we report our experience of eight patients with splenic tuberculosis in whom the diagnosis could only be established after histopathological examination of the removed spleen.

MATERIALS AND METHODS

Between January 1989 and December 2008, 339 patients underwent splenectomy for various indications other than trauma at our centre, a tertiary referral hospital in northern India (Table 1). In 77 (23%) patients, splenectomy was primarily performed for diagnostic purposes. Eight of

Table 1. Indications for Splenectomy

Indication	No. of patients (n=339)
Steroid resistant ITP	113
Thalassemia	87
Hereditary spherocytosis	40
Autoimmune hemolytic anemia	11
Splenomegaly of undiagnosed etiology	77
Other lesions	11

ITP, idiopathic thrombocytopenic purpura.

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77 patients who had a diagnosis of tuberculosis on histopathological examination of the splenectomy specimens were retrospectively analyzed for their clinical presentation, management and outcome. Information was collected from the computerized hospital information system and hand written medical records. All attempts were made to identify the cause for fever and splenomegaly before subjecting these patients for splenectomy. All patients underwent full hemogram, liver function tests, chest X-ray and abdominal ultrasonogram (USG). Bone marrow biopsy and ELISA test for HIV were performed in all patients as well. Contrast enhanced computerized tomogram (CECT) of the abdomen was done in four patients to further characterize the splenic lesions. As per our protocol, patients received pneumococcal vaccine before splenectomy. During splenectomy, liver tissue was also sampled for biopsy along with lymph nodes if enlarged. Specimens were subjected to routine histopathologic evaluation. Tissue sections were subjected to acid-fast bacilli (AFB) staining with 0.2% Ziehl-Neelsen stain to look for mycobacteria. Periodic acid Schiff (PAS) and chromic acid methenamine silver (CSM) stains were used for identification of fungal elements.

Splenomegaly was graded based upon the enlargement of the spleen in centimeters below the left costal margin (mild- up to 5 cm, moderate- between 5 and 10 cm, gross- more than 10 cm).⁷ Hypersplenism was defined as the presence of at least two cytopenias (anemia- hemoglobin <10 g/dL, leucopenia-total leukocyte count <4,000/uL, thrombocytopenia- platelet count <1.5×10⁵/mm³) along with a normal or hypercellular bone marrow. Reversal of hypersplenism was defined as the normalization of all the three cytopenias above the upper limits defined for hypersplenism, within one month of splenectomy.⁸

RESULTS

A diagnosis of tuberculosis was established in 10%

Table 2. Clinical Features in Patients with Splenic Tuberculosis

Clinical features	No. of patients (n=8)
Fever	8
Splenomegaly	8
Hepatomegaly	7
Lump in abdomen	5
Pallor	4
Gastrointestinal bleeding	3
Pain abdomen	2
Jaundice	2
Weight loss	2

(8/77) of patients who underwent diagnostic splenectomy. There were six males and two females whose age was between 19 and 53 years. All patients were referred from peripheral hospitals for the workup of fever of unknown origin (FUO). Five of them were further investigated for the cause of pyrexia in the Immunology and Hematology services of our hospital, and were later referred to us for diagnostic splenectomy. Three patients were referred with a diagnosis of splenic abscess from the Gastroenterology department. Table 2 summarizes the clinical features in these patients. Splenomegaly was gross in five patients and moderate in three. Two patients presented with melaena and one with hematemesis. Hemogram revealed hypersplenism in three patients. Bone marrow biopsy demonstrated hyper cellular marrow in two patients and appeared to be normal in others. Chest X-ray was normal in all patients. Abdominal USG revealed multiple small hypoechoic lesions in the spleen in three patients and multiple abscesses in two. The other three patients had no splenic lesions on USG. Abdominal CECT revealed multiple hypodense lesions in the spleen in two and confirmed splenic abscesses in the other two patients. Three patients had ascites on USG. Four patients underwent esophagogastroduodenoscopy (EGD) to rule out portal hypertension as the cause of splenomegaly; one had isolated gastric varices. Anti-HCV antibody, HBsAg and ELISA for HIV were negative in all patients. One patient with splenic abscess underwent percutaneous drainage of the abscess that did not result in the resolution of the disease. Aspiration cytology of the splenic lesion was done in another patient and it revealed caseating granulomas (Fig. 1). Microscopic examination for AFB and AFB culture from the splenic aspirate were negative in both these patients.

Fig. 1. Epithelioid granuloma (thin arrow) with background necrosis (thick arrow).

Fig. 2. Cut section of explanted spleen: multiple caseating nodules.

All patients underwent open splenectomy. Multiple white caseating nodules in the spleen were seen in three patients (Fig. 2). Two patients had solitary abscesses in the spleen and the other two patients had subcapsular infarcts. Other associated findings were enlarged splenic hilar lymph nodes ($n=7$), enlarged cystic lymph node ($n=1$), paraaortic lymph nodes ($n=2$) and ascites ($n=3$).

On histopathologic examination, all the splenectomy specimens showed epithelioid granulomas composed of aggregates of epithelioid cells, lymphocytes and Langhans giant cells with variable degree of central caseous necrosis involving both the red and white pulps (Fig. 3). In five patients, splenic hilar lymph nodes showed caseating granulomas. Liver tissue and cystic lymph node also showed tuberculous granulomas in one patient respectively. Splenic tissue staining for AFB and fungal elements were negative in all patients. In the postoperative period, two patients had lower respiratory tract infection and sputum stain and culture showed positive for tubercle bacilli.

Splenectomy reversed the hypersplenism in all three patients who had cytopenias before splenectomy. All patients received antituberculous drugs for a period of six months post-operatively. With a mean follow up of 36.4 months (7-72 months), all patients were doing well till the last follow up.

DISCUSSION

Abdomen is affected in 11% of patients with extrapulmonary tuberculosis.⁹ Bhansali *et al.*,¹⁰ in a series of 300 patients with abdominal tuberculosis, did not encounter even a single case of splenic tuberculosis. Most of the experience with splenic tuberculosis included patients

Fig. 3. Tubercular granuloma: central caseating necrosis (thick arrow) and Langhans giant cells (thin arrow).

who were immunocompromised or with miliary tuberculosis. The incidence of splenic tuberculosis may be variable depending on the prevalence of the disease in a particular geographical area. Simu *et al.*¹¹ reported a 4% of tuberculosis in patients subjected to a diagnostic splenectomy compared to 12% in the present series, which could reflect a tertiary care referral bias.

Splenic tuberculosis as a cause of FUO had been reported earlier.^{12,13} Contrary to the reported literatures which considered tuberculosis as a cause of mild splenomegaly,⁷ most of our patients had massive splenomegaly. Tuberculosis could also present as hypersplenism with bleeding manifestations.¹⁴ Late detection of the disease at the stage of hypersplenism might explain the massive splenomegaly in our patients. Perisinusoidal inflammation and perisinusoidal fibrosis may develop in relation to tubercular granulomas, which may lead to progressive obstruction to venous drainage that may further result in splenomegaly and hypersplenism. On USG, splenic tuberculosis usually presented as multiple small hypoechoic lesions^{1,6} and CECT may demonstrate hypodense lesions.^{3,6,15} Tuberculosis has been reported as a rare cause of splenic abscess.³ The reported yield of aspiration cytology from the splenic lesions is variable. Suri *et al.*¹⁶ reported up to 88% sensitivity for fine needle aspiration cytology (FNAC) for diagnosing a tuberculous pathology in the spleen. AFB staining of tissue sections was negative in all of our patients. Fukunaga *et al.*¹⁷ reported that, tubercle bacilli were frequently missed or underestimated with acid fast microscopy on formalin fixed, paraffin embedded tissues.

Tubercular involvement of the spleen is commonly reported in miliary tuberculosis. Seven of eight patients in our series showed extrasplenic involvement. None of our

patients were found to have any evidence of other systemic disease or immunodeficiency during the diagnostic work up.

Clinical presentation with FUO and splenomegaly warranted splenectomy for diagnosis in most of the reported experience of splenic tuberculosis. If a definite diagnosis can be made without splenectomy, splenic tuberculosis can be treated with antituberculous therapy alone.^{12,18,19} Contradictory reports are also available favoring absence of response to antituberculous therapy without splenectomy.²⁰

Tuberculosis should be considered as one of the differential diagnosis in patients presenting with FUO and splenomegaly especially in areas where the disease is prevalent. Splenic tuberculosis can even affect immunocompetent individuals. Extrasplenic involvement frequently occurs in splenic tuberculosis. In patients presenting with FUO and splenomegaly, where an exact diagnosis could not be established after all possible and available investigations, splenectomy is strongly recommended for the diagnosis and further treatment. Empirical exposure to antituberculous drugs could be hazardous in these situations as it may mask a definite diagnosis later. At times such patients may not respond to antituberculous drugs and require splenectomy subsequently.

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