

CASE REPORT

Bone marrow cryptococcosis: a case report

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Abstract

A 35-year-old male presented with fever and bilateral cervical and axillary lymphadenopathy. Peripheral blood film examination revealed thrombocytopenia. Bone marrow aspiration and trephine biopsy, done for evaluation of thrombocytopenia and pyrexia showed presence of ill-defined granulomas along with cryptococcal yeast forms. Fine needle aspiration of lymph nodes, cerebrospinal fluid and sputum analyses also showed cryptococci. ELISA for Human Immunodeficiency Virus (HIV) antigen was positive.

Granulomas, when found in bone marrow aspiration smears and trephine biopsy, are a valuable histological clue to an opportunistic infection. Disseminated fungal infection such as cryptococcosis should raise the possibility of immunosuppression, especially Acquired Immunodeficiency Syndrome. Bone marrow examination is a useful method of diagnosing opportunistic fungal and mycobacterial infections in patients with fever, anaemia or thrombocytopenia and underlying HIV infection.

Key words: Cryptococci, Bone marrow biopsy, Granuloma, Acquired Immunodeficiency syndrome

INTRODUCTION

Granulomas are an infrequent finding in bone marrow trephine biopsies.¹ Several diseases are associated with the formation of granulomas in the marrow. These include fungal and viral infections, tuberculosis, sarcoidosis, connective tissue disorders, lymphomas and metastatic carcinoma.^{1,2} Cryptococcal infection occurs commonly in patients with immunosuppression. It frequently involves either the lung or the central nervous system.^{3,4} Disseminated cryptococcosis is relatively uncommon and most of these occur in patients with severe immunosuppression, commonly as a result of Acquired Immunodeficiency Syndrome (AIDS)^{3,4,5,6} but a few cases have been reported to occur in idiopathic CD 4-T cell lymphocytopenia.⁷

We report a case of disseminated cryptococcosis with granulomatous reaction in bone marrow. It was the initial manifestation in a patient who subsequently tested positive for Human immunodeficiency Virus (HIV).

CASE REPORT

A 35-year-old male agricultural labourer presented with left-sided headache of four months duration, cough with mucopurulent expectoration of one-month duration and fever for the past ten days.

On examination, he was found to have pallor, cyanosis and clubbing of fingers. Oral cavity showed white patches. Multiple, bilateral cervical and axillary lymph nodes were enlarged, the largest measuring 2x2 cm. The nodes were rubbery, non-tender and mobile. Examination of the respiratory system revealed bilateral basal crepitations. Liver and spleen were not palpable. Neurological examination revealed meningeal signs.

Initial blood counts showed a haematocrit of 25%, white blood cell count of $7.5 \times 10^9/L$ with 88% neutrophils, 10% lymphocytes and 2% eosinophils. The platelet count was $19 \times 10^9/L$. The ESR was 62 mm at the end of the first hour.

A bone marrow aspiration and biopsy was advised as an investigation for pyrexia and

thrombocytopenia. Bone marrow aspirate showed hypercellular marrow particles. Erythropoiesis was normoblastic and myeloid cells showed toxic granulations. A good number of macrophages, plasma cells, lymphocytes and a few scattered epithelioid cells along with cryptococcal yeast forms were demonstrable. Bone marrow trephine biopsy showed a hypercellular marrow with plasmacytosis and megakaryocytosis. In addition, there were a few epithelioid-cell granulomas (Fig. 1). Many cryptococcal yeast forms were seen within these granulomas (Fig. 2). The fungi were demonstrated by Periodic Acid Schiff and Mucicarmine stains. A moderate increase in fibrosis was also noted.

Fine needle aspiration and biopsy of cervical and axillary lymph nodes revealed features of cryptococcal lymphadenitis. There was diffuse effacement of the nodal architecture with the presence of numerous histiocytes. Many cryptococci were seen. Mucicarmine stain highlighted the capsulated yeast forms of cryptococci.

Fundoscopy showed bilateral retinal haemorrhages and soft exudates. KOH mount of the white patches in the oral cavity was positive for candida. Chest radiography showed bilateral miliary mottling. Cerebrospinal fluid (CSF) analysis showed the presence of

cryptococci, as did the sputum sample. Stain for acid-fast bacilli were negative in all the specimens. *Cryptococcus neoformans* was isolated from blood and CSF culture.

On specific questioning, the patient revealed contact with a commercial sex worker in the past. ELISA test for the detection of HIV was positive. A diagnosis of disseminated cryptococcosis in Acquired Immunodeficiency Syndrome was made. The patient was treated with Amphotericin and oral Fluconazole and was advised to come for regular follow-up.

DISCUSSION

Current day medical practice involves a routine battery of tests in the evaluation of a patient, especially HIV positive, who present with pyrexia of unknown origin.⁸

Bone marrow aspiration and trephine biopsy, which are among the usual tests done in investigating such patients showed, in our case, the presence of epithelioid cells in the aspiration smears and granulomas in the trephine biopsy. Granulomas in bone marrow aspiration smears are an extremely rare finding. The detection rate is much higher in a trephine biopsy than in an aspiration smear.^{9,10} The increased reticulin deposition associated with granuloma formation often means that there is a dry tap or only a

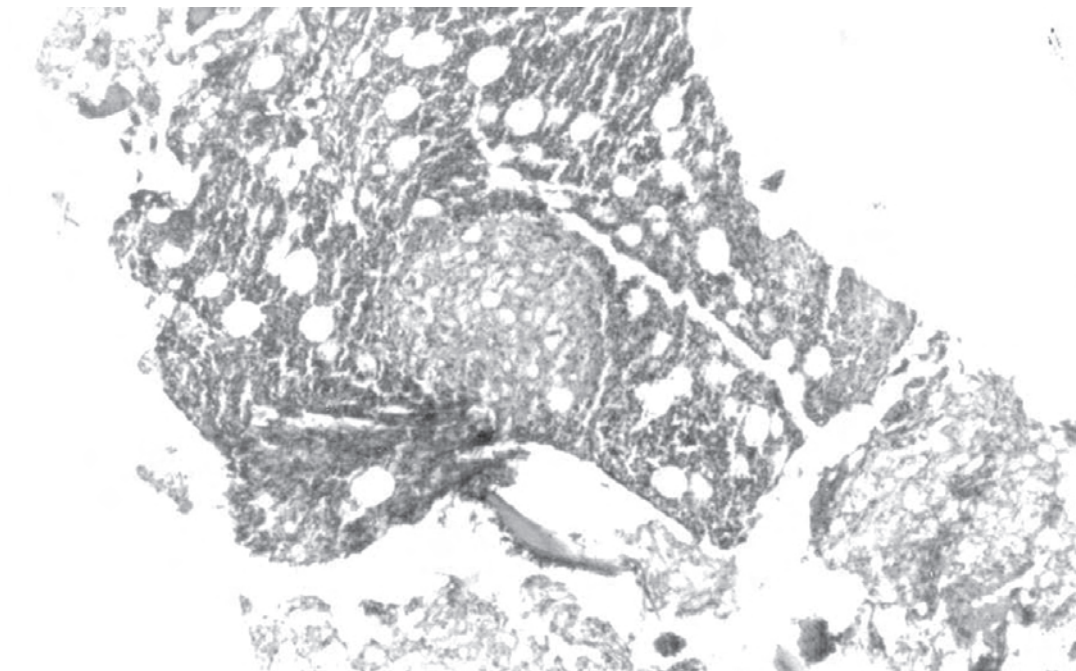


FIG. 1: Epithelioid cell granuloma in bone marrow trephine biopsy (H&E X 100)

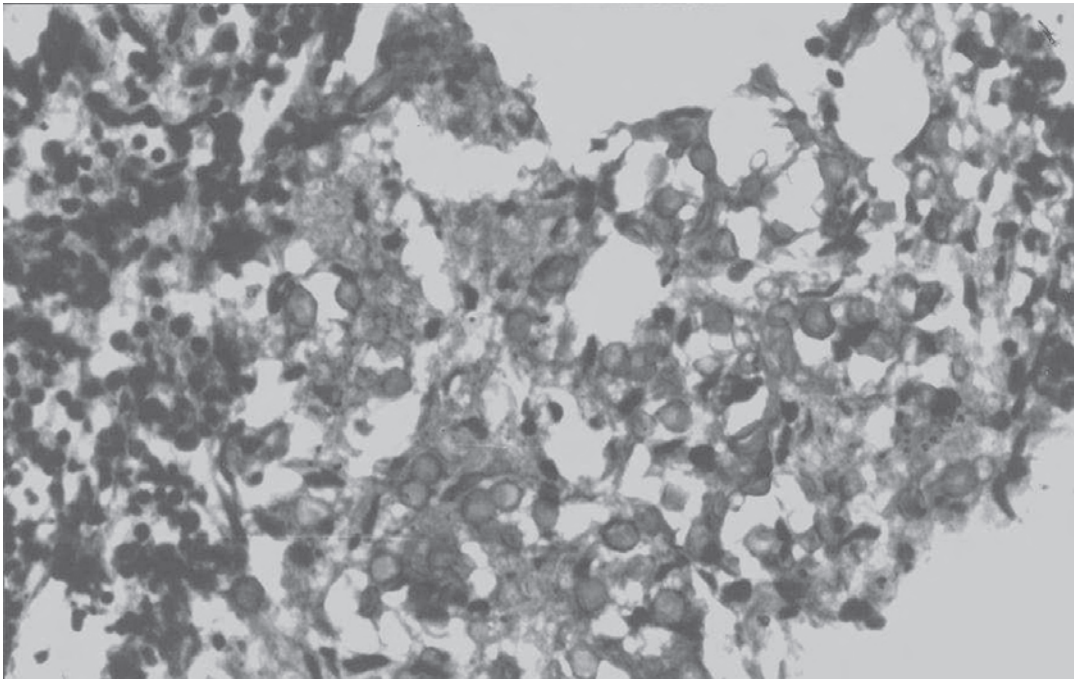


FIG. 2: High power view of the granuloma with cryptococcal yeast forms highlighted. (Mucicarmine X 400)

relatively scant amount of normal marrow is aspirated.⁹

Granulomas when found in bone marrow aspiration smears or trephine biopsy require definition as to an underlying aetiology.¹ They are a valuable histological clue to an opportunistic infection.¹¹ As with other tissues, special stains for acid fast bacilli and fungi should be performed in all cases of marrow granulomas.^{11,12} By combining careful histological, microbiological and serological technique, an aetiology can be documented in most patients with marrow granulomas. In our case, cryptococci were visible on careful search of the Romanowsky-stained aspiration smears and the Haematoxylin-Eosin stained biopsy. Mucicarmine and other special stains were used to highlight and confirm the presence of the fungi. Usually the diagnosis of cryptococcosis rests on spinal fluid studies and little attention has been paid to the direct examination of a bone marrow specimen. Visualization of the fungi in bone marrow specimen could be useful in the initial examination of febrile patients with neoplastic disease and/or compromised host defenses and would permit early institution of specific therapy.¹³

Cryptococcus, as a cause of bone marrow granuloma, should raise the possibility of immunosuppression, especially AIDS. The yeast

forms of cryptococcus stimulate a granulomatous response in all cases despite immunosuppression. The number of cryptococcal organisms appears to be inversely proportional to the adequacy of the granulomatous response.¹⁴ Typical epithelioid-cell granuloma may not be present in the marrow of immunocompromised patients with disseminated mycobacterial or fungal infection.¹² Infection of bone marrow with cryptococci may act in synergy with the HIV to cause cytopenia,¹⁴ as was seen in our case, who had a low haematocrit and thrombocytopenia.

In our case, cryptococci were seen in lymph nodes, cerebrospinal fluid and sputum in addition to bone marrow. Widespread involvement by cryptococcus of lungs, bone marrow, gastrointestinal tract, skin and lymph nodes have been reported and most of these cases are in patients with AIDS.^{3,4,5,6,13} Cryptococcosis has also been reported in idiopathic CD-4 T-cell lymphocytopenia.⁷ The polysaccharide capsule of *Cryptococcus neoformans* is immunosuppressive, possibly resulting in low CD-4 lymphocyte counts.¹⁵

The evaluation of bone marrow in diagnosing an infective aetiology led us to the initial presentation of a patient with AIDS. Bone marrow examination can be a useful method of diagnosing opportunistic fungal and mycobacterial infections in patients with fever,

anaemia or thrombocytopenia and underlying HIV infection.

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