**Case Report**

**Epitheloid granuloma of bone marrow- not always tuberculosis, think beyond what you see**

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**ABSTRACT**

Extra pulmonary tuberculosis has varied presentations and hence fever of unknown origin, with malaise, weight loss and cytopenias is generally attributed to tuberculosis in endemic regions. Tuberculosis being the most frequent cause of bone marrow granulomas, there is a risk of labelling granulomatous lesions as of infectious etiology when underlying etiology has an atypical presentation. Progressive painless lymphadenopathy, most commonly involving the cervical or supraclavicular area is the commonest presentation of Hodgkin’s lymphomas (HL) in 80%. Primary extra nodal presentation of HL is rare. We describe a case of an adolescent girl who presented with fever of unknown origin, weight loss, malaise, hematological derangements and bone marrow showing granuloma, all features pointing towards an infectious etiology, but later proven to be a case of HL.

**Keywords:** Fever of unknown origin, Bone marrow biopsy, Epithelioid granuloma, Hodgkin lymphoma

**INTRODUCTION**

Painless progressive peripheral lymphadenopathy is the common clinical presentation of Hodgkin lymphoma (HL). Non-specific constitutional symptoms like fatigue, anorexia, weight loss, pruritus, night sweats and fever occur in 25%. Extra nodal involvement has been reported in 15-20%. The most common sites involved are lung, liver, bones and bone marrow. But, primary extra nodal presentation of Hodgkin’s lymphoma occurs in <0.25%.¹ Bone marrow granuloma has been reported in 5% of HL.²

We report a case of a 14-years-old girl who presented with epithelioid granuloma of bone marrow as the primary extra nodal manifestation of Hodgkin lymphoma.

**CASE REPORT**

A 14-years-girl presented with history of fatigability, weight loss and high-grade fever with drenching night sweats for three months. There was no history of mucocutaneous bleeds, bone pain or joint pains. She also gave a history of loss of 6 kgs over last three months. There was no contact history of tuberculosis. On examination she had pallor, but no palpable peripheral lymphadenopathy or hepatosplenomegaly. Investigations revealed a hemoglobin of 7.7 g/dl, total leukocyte count- 1900 cells/cumm; platelets-1.67×lakhs/cumm; ESR-84 mm/hr; normal reticulocyte count and X-ray chest was normal. She was evaluated for tuberculosis, typhoid fever, EBV, CMV and brucellosis and no infective etiology could be confirmed. Hemophagocytic lymphohistiocytosis work up was normal. Auto-immune work up showed direct coombs test- negative, antinuclear antibodies (ANA)- negative and normal C3 and C4 levels. In view of cytopenias and persistent fever spikes, bone marrow aspiration and biopsy were done which revealed a hypocellular marrow showing an ill-defined epithelioid granuloma (Figure 1). As common infectious etiologies were ruled out, further evaluation with whole body PET CT revealed multiple
focal FDG avid lesions diffusely scattered in the bones involving the entire spine, bilateral scapula, sternum, bilateral ribs, bilateral femur and tibias, left talus and left cuboid, max SUV - 5.95 in right iliac bone and multiple FGD avid enlarged lymph nodes in the para aortic/aorta caval (1x10.6 cm), bilateral external iliac (1.7x1.1 cm), right para tracheal (4x3.3x2.7 cm), lower cervical/ supra clavicular (1x1 cm), left axillary (1.9x1 cm) and left para tracheal/subcarinal/left inter lobar regions (1x1.7 cm) with max SUV 6.3 in right paratracheal lymph node region suggestive of disseminated malignancy. By immuno histochemistry the bone marrow biopsy was positive for CD 15, CD 30, PAX5 and focally for EBV LMP (latent membrane protein), confirming the diagnosis of classic HL - mixed cellularity type (Figure 2). She was started on HL Euronet protocol (OEPA regimen - vincristine, etoposide, prednisolone, doxorubicin). Fever subsided and her symptoms improved after first week of chemotherapy. She has gained 2 kg over 1 month and has completed 2 cycles of chemotherapy and PET for interim response assessment showed a complete response.

DISCUSSION

Extrapulmonary tuberculosis presents with varied clinical picture such as pyrexia of unknown origin, hepatosplenomegaly, lymphadenopathy meningitis and hematological manifestations like anemia, leukopenia, thrombocytopenia, leukocytosis, monocytosis, thrombocytosis and rarely pancytopenia. In endemic regions, patients presenting with pyrexia of unknown origin, malaise and weight loss and peripheral cytopenia are labelled as disseminated tuberculosis. When bone marrow biopsy done for infectious etiology shows a granulomatous lesion, they are generally started on Anti Tuberculous therapy after ruling out other common infectious causes. The incidence of bone marrow granuloma ranges from 0.38% to 2.2%. Granuloma formation is an uncommon finding in bone marrow examination with an incidence of 0.35-2.2%. Granuloma consists of clusters of epithelioid histiocytes, lymphocytes and giant cells. It is a non-specific finding encountered in infectious as well as non-infectious conditions like autoimmune conditions and drugs such as procainamide, sulfonamide, chlorpropamide, phenylbutazone, phenytoin and methyldopa. Tuberculosis is the prototype, constituting 6-48% of the cases. Typhoid fever, brucellosis, sarcoidosis, viral infections such as CMV and EBV, fungal infections like histoplasmosis have also been reported. Malignant conditions causing granulomas in bone marrow, such as HL, non-HL, lung carcinoma, ovarian carcinoma, colon carcinoma, acute myelocytic leukemia, chronic myelocytic leukemia have been reported in 20-25% cases and HL being more frequent.

There are no morphologic features that provide a reliable differentiation between various causes of bone marrow granuloma. A meticulous history, microbiological, serologic and histologic tests will help in arriving at the diagnosis in most of the cases.

Atypical presentation of HL with epithelioid granuloma formation has been reported. These granulomas may precede the onset of primary malignancy and in such cases, leads to delay in diagnosis. They may occur at the site of primary tumor or at distant organs or draining lymph nodes without any evidence of malignancy. Typical Reed-Sternberg cells are rare in bone marrow aspirates. In lymphomas, the bone marrow granuloma could be due to invasion of the bone marrow or due to non-specific immunologic change due to malignancy.

Histological indicators of HL in bone marrow includes Reed-Sternberg cells or their variants in a polymorphous cellular background, myelonecrosis, focal fibrosis, myxoid change and granulomas.

Lymphomas may be misdiagnosed as infectious disease when they present with fever and weight loss and without significant peripheral lymphadenopathy. Bone marrow
examinations in such cases are usually done to investigate the infectious cause of fever and cytopenias. Though malignant conditions are known to be associated with granulomas, initial detection of granuloma without any evidence of malignancy, leads to longer diagnostic work up and mostly ends in treating with anti-tubercular drugs and steroids. As lymphomas and tuberculosis share the clinical features, when tuberculous etiology is not confirmed, bone marrow examination supported by immunohistochemistry helps in diagnosis.

CONCLUSION

Tuberculosis still remains the most common cause of bone marrow granulomatous lesions. The high frequency of tuberculosis in India, might lead to a risk of all granulomatous inflammations to be presumptively labeled as tuberculosis, thereby causing a delay in the diagnosis of the actual underlying infection or neoplasm.

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