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CASE REPORT Open Access

Isolated bone marrow sarcoidosis presenting as fever of unknown origin in a case of chronic myeloid leukemia

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Abstract

Background: Isolated involvement of bone marrow in sarcoidosis has not been reported commonly. Sarcoidosis is a systemic granulomatous disease of unknown origin, characterized by the presence of non-caseating granulomatous lesions. There should be high index of suspicion in patients having underlying lymphoproliferative malignancies.

Case presentation: We present a 27-year-old male, known case of chronic myeloid leukemia, presenting as fever of unknown origin diagnosed with isolated bone marrow sarcoidosis.

Keywords: Sarcoidosis, Fever of unknown origin, Extra pulmonary manifestation of sarcoidosis, Chronic myeloid leukemia

Introduction

Sarcoidosis is a systemic ubiquitous disease, granulomatous, of unknown origin, typically characterized by the presence of non-caseating granulomatous lesions with pulmonary findings in more than 90% of the patient's [1]. Sarcoid disease can occur either in association with or even in the absence of intra thoracic disease [1]. The occurrence of only extra pulmonary sarcoidosis without any pulmonary involvement is only up to 10% of all cases [1]. Interestingly, although pulmonary involvement is most common, the cause of morbidity is usually extra pulmonary manifestations of the disease [2]. We encountered a case of isolated sarcoidosis of the bone marrow presenting as fever of unknown origin in a patient with chronic myeloid leukemia.

Case report

A 27-year-old man, presented with a history of recurrent fever for the past 4 months, fever spikes showing a nocturnal preponderance and lasting for 5–6 days, with no significant associated symptoms. He was a diagnosed case of chronic myeloid leukemia and was on follow-up treatment with the medical oncologist. Physical examination was unremarkable. Laboratory studies showed Hb 13.7 g/dl, Total leucocyte count was 3.84 × 10^9/L, platelet count 152 × 10^9/L, differential leucocyte count revealed neutrophil 49%, lymphocyte 41%, monocyte 7%, eosinophil 1%, basophil 2% with peripheral smear had normocytic normochromic R.B.C., mild leukopenia and adequate platelet. Liver function test revealed normal albumin, globulin, and enzymes (albumin 4.8 g/dl, globulin 2.6 g/dl, SGOT 38 U/L, SGPT 42 U/L) with raised alkaline phosphatase (ALP 138 U/L). Renal function test showed normal level of serum urea and creatinine (urea 15.3 mg/dl, creatinine 0.8 mg/dl). Acute phase reactants were sent which revealed elevated ESR (27 mm/h), C.R.P. (16.2 mg/L), normal ferritin (272 ng/ml), and triglyceride (178 mg/dl). Urinalysis revealed no pus cells, no cast and R.B.C with mild proteinuria. Peripheral smear for malaria parasite, malaria antigen, and typhi dot were negative. Blood and urine culture were also sterile. Autoimmune workup (ANA, RF) and HIV were done which were negative. Contrast enhanced CT chest and abdomen revealed mild splenomegaly (13 cm). BCR-ABL Quantitative IS

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RQ, real-time PCR was also negative. Further workup for fever was done, and Mantoux test, quantiferon TB gold, Weil-Felix test, scrub typhus IgM, and Widal test were sent which were negative. Bone marrow biopsy was done which revealed normoblastic to mildly megaloblastoid maturation with mild dyserythropoiesis in erythroid series, myeloid series showed adequate maturation with blast count < 1% of total nucleated cells, adequate megakaryocytes with unremarkable morphology, with no abnormal cell/hemoparasite. Flow cytometry and immunophenotypic analysis did not revealed any evidence of acute leukemia or lymphoma. Fluorescence in situ hybridization was negative for myelodysplasia. AFB smear and GeneXpert were negative and AFB, pyogenic cultures was sterile. Few ill-defined and well-defined confluent epithelioid cell granulomas with no necrosis were seen amidst reactive cellular population (Fig. 1). Serum A.C.E. was done in view of bone marrow finding, which was elevated (231.8 U/L), suggestive of sarcoidosis. MRI head and spine was done to exclude neurosarcoidosis. In view of recurrent febrile episodes, raised serum A.C.E. level and non-caseating granulomatous lesion were observed in the bone marrow, and he was started on oral prednisolone 60 mg daily which was gradually tapered to 20 mg twice daily after 4 weeks since initiation of steroid therapy. Patient became afebrile and did not have any recurrent episode of fever. A diagnosis of isolated bone marrow sarcoidosis was made. His serum A.C.E. level was 43 U/L, 4 weeks after starting oral prednisolone. He has been afebrile and well at the last follow-up 6 months after stopping treatment.

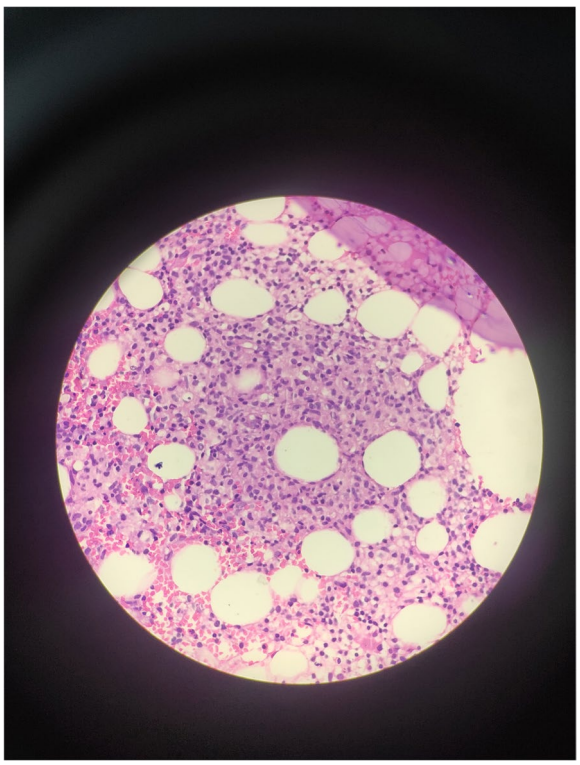

Fig. 1 Few ill-defined and well-defined confluent epithelioid cell granuloma with no necrosis amidst reactive cellular population

Discussion

Sarcoidosis is a systemic granulomatous disease with varying pulmonary and extrapulmonary manifestations histologically characterized by non-caseating epithelioid granuloma [3]. Pulmonary involvement is found in more than 90% of patients. Extra pulmonary manifestations can be subtle but may significantly contribute to morbidity and mortality [4]. Bone marrow sarcoidosis is a rare finding, and no case series have been reported from India. Although the association of sarcoidosis with lymphoproliferative malignancies has been well documented, the commonest being the presence of Hodgkin's disease [5]. Conversely, patients who are already diagnosed to have sarcoidosis may go on to develop hematological malignancies, the basis for which is aneuploidy in the granuloma cells as well as peripheral blood lymphocytes, thereby creating a genetic instability, leading to hematologicalmalignancies [6]. A thorough history-taking and physical examination remain important along with a high index of suspicion. The commonest hematological abnormality in sarcoidosis (with or without bone marrow involvement) is anemia which may be either iron deficiency anemia or hemolytic anemia or anemia of chronic disease [7]. Leukopenia may be the only initial presentation which may be either due to bone marrow infiltration or hypersplenism and lymphocyte redistribution [8, 9]. Bone marrow sarcoidosis can even present with cytopenias [8, 9]. One patient had mild anemia and mild leukopenia. Thus, in the absence of occurrence of hematological abnormalities, the diagnosis of bone marrow sarcoidosis may not be made except through a high index of clinical suspicion. Incidence of non-caseating granuloma lesions in bone marrow biopsy is of the order of 0.3–2.2% [10]. The differential diagnoses which need to be considered in each case are solid tumor, lymphomas, Wegener's granulomatosis, Farmer's lung, Bird Fancier's lung (hypersensitivity pneumonitis), primary biliary cirrhosis, occupational exposure to beryllium and talc, and infections (atypical mycobacteria, fungi) [10, 11]. Splenomegaly can occur in about 25% of patient of sarcoidosis [11]. Hepatic involvement can occur in 20–30% of the patient's affected by sarcoidosis [11]. Neurological complication of sarcoidosis include cranial neuropathy {meningeal disease and cord compression syndrome (incidence is 3-10%)} [12]. One patient had mild splenomegaly with no neurological involvement, borderline

anemia and leukopenia with isolated granulomatous lesion in bone marrow.

Steroids remain the mainstay of treatment in bone marrow sarcoidosis, so in selected cases adalimumab can be used [13]. Methotrexate has restricted use for bone marrow sarcoidosis because of its potential cytotoxic effects on the bone marrow [13]. Our patient responded well to oral steroid (prednisolone).

Conclusion

Isolated bone marrow sarcoidosis is rare and can be a diagnostic challenge. There should be a high index of suspicion for patients who have underline lymphoproliferative malignancies. Because of the rarity of the bone marrow sarcoidosis, it is not known about long-term outcome so we recommend surveillance and regular follow-up in view of possibility of other systemic involvement or progression of sarcoidosis or flare up of malignancy, since there is a well-documented association between lymphoproliferative/hematological malignancies and sarcoidosis.

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SP: manuscript preparation. AKG: clinician. SC: editing. MM: data collection. PCM: proofreading. All authors read and approved the final manuscript.

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Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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