Bone marrow granuloma in a child with pyrexia of unknown origin: A clue for diagnosis of brucellosis

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Bone marrow culture and biopsy are an integral part of investigations in children with pyrexia of unknown origin (PUO). Granulomatous lesions are uncommon findings in bone marrow and only a few diseases are associated with them. Brucella is an uncommon cause of granuloma formation in the bone marrow. Diagnosis of brucellosis is often delayed because of low clinical suspicion in non-endemic areas.

A 7-year-old boy presented with fever for 2 months. There was no history of cough, dyspnea, rash, anorexia, weight loss, bleeding manifestations, eschar, arthralgia or bone pain and his parents confirmed no recent travel, contact with tuberculosis or exposure to pets or farm animals. He had received oral and intravenous antibiotics at outside clinics. On examination, subcentimetric cervical lymph nodes and hepatosplenomegaly 4 and 3 cm below respective costal margins were noted. Other systemic evaluation was unremarkable.

Hemoglobin was 11.5 gm/dl; total leukocyte count was 9.2 x 10⁹/L with 69% neutrophils and 25% lymphocytes. Platelet count was 278 x 10⁹/L and the peripheral blood smear was normal. Peripheral smears and immunochromatographic test for malaria, blood culture, Widal test, rK39 antigen, Mantoux test, sputum for acid-fast bacilli (AFB) and serology for Epstein barr virus and parvovirus were negative. Contrast-enhanced CT (CECT) chest was normal and CECT abdomen confirmed hepato-splenomegaly. Anti-nuclear antibodies, rheumatoid factor and serum ferritin were negative/normal.

Bone marrow was normocellular and the trephine biopsy revealed very few well-defined epithelioid granulomas [Figure 1a] as well as tiny, ill-defined paratrabecular collections of epithelioid histiocytes [Figure 1b] in a few sections. However, no caseous necrosis or giant cell formation were seen. Stains for AFB and fungi were negative. Brucella standard tube agglutination test and serology were positive (Brucella IgM ELISA 1:2560 titer). Subsequently, blood culture on prolonged incubation showed growth of Brucella melitensis. The child was treated with intravenous gentamycin for 2 weeks and oral rifampicin and trimethoprim-sulfamethoxazole for 4 weeks. Fever subsided in a week. On follow-up, hepatosplenomegaly regressed and titers for Brucella serology declined.

Granulomatous inflammation represents a distinctive chronic inflammatory pattern characterized by focal accumulation of activated macrophages, which often develop an epithelioid appearance. It is non-specific, encountered in immune-mediated, infections and non-infectious conditions. Tuberculosis is the prototype, however typhoid fever, sarcoidosis, brucellosis, and malignancies like Hodgkin and non-Hodgkin lymphomas can also be associated with a granulomatous reaction. Naseem et al. reported only two cases of granulomatous reaction in 990 bone marrow studies performed for evaluation of bicipitopenia or pancytopenia in children. The high frequency of tuberculosis in India leads to a risk of all granulomatous inflammations to be presumptively labelled as tuberculosis, which may delay the diagnosis of the actual underlying infection or neoplasm.
Brucellosis in children presents with osteo-articular manifestations in 70% and with non-specific fever in 20%. In a large series of childhood Brucellosis, the most common clinical manifestations reported were fever, joint pain, and hepatomegaly. Blood culture is the gold standard for diagnosis but its use is limited because of delayed growth of the organism resulting in low sensitivity that is further reduced by prior empirical antibiotic use. Hematological manifestations of Brucellosis include anemia, leucopenia, lymphocytic leukocytosis and rarely with thrombocytopenia, pancytopenia. Bone marrow findings in cases complicated by pancytopenia include normocellular or hypercellular marrow, granulomas, hemophagocytosis, rarely myelofibrosis and hypoplasia. The incidence of Brucella as cause of granulomatous lesions in bone marrow is reported to usually be between 0% to 25% in various case series. Granulomas in Brucella are typically small, with epithelialized cells surrounded by a few lymphocytes and plasmacells. Hemophagocytosis may occur, but caseating necrosis is typically absent.

In conclusion, Brucellosis is a rare but important infectious cause of granulomatous lesions in the bone marrow as well as an important and treatable cause of PUO even in non-endemic areas. Rare, small-sized non-caseating granulomas, as in our case represent important diagnostic clues and pathologists should employ serial sections to confirm their presence/absence.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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