



TYPHOID FEVER MASQUERADING AS BONE MARROW GRANULOMA: A DIAGNOSTIC DILEMMA

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Abstract

Typhoid is among the seldomly observed etiology of granuloma in bone marrow despite of very high prevalence of typhoid globally. Here we provide a brief overview of a case of a young male with fever, dry cough, splenomegaly with bicytopenia. Typhoid fever, especially in areas with high prevalence, should be considered as an important differential diagnosis of bone marrow granuloma in patients with prolonged or unexplained pyrexia and in those who have travelled to endemic areas making it important to rule out all other possibilities before starting anti tubercular therapy.

Introduction

Typhoid is caused by Salmonella, a gram-negative, flagellate, rod shaped bacterium which belongs to the Enterobacteriaceae family. In year 2017, S. typhi and S. paratyphi has been estimated to have caused 14.3 million instances of salmonella infection around the globe, out of which about 75 percent of all cases and 120,000 deaths were because of S. typhi alone.^[1] Most common presentation of typhoid is fever with intestinal discomfort in form of constipation, loose stool, abdominal pain etc but various non intestinal features has also been reported like CNS involvement (3–35% cases), Cardiac involvement in 1–5% cases, respiratory involvement (1-85% cases), hepatic involvement (1-26% cases), bony and genitourinary involvement (<1% cases).^[2] Here we provide a brief overview of a case of blood culture proven typhoid fever with an extra intestinal atypical presentation in form of a non-caseating granuloma in bone marrow.

Case Presentation

A 26 years old Indian male presented with complaints of fever and dry cough for the last seven days. Fever was documented to be 102⁰F with evening rise of temperature and was associated with dry cough. Fever intermittently was relieved by consumption of antipyretic medication. There were no history of night sweats, shortness of breath, pain abdomen and altered bowel habits, burning micturition, weight loss, abnormal body movements, pus discharge from any site, sore throat, rash, chest pain, palpitations, oral ulcer and joint pain.

On examination patient was found to be average built person. Patient was febrile (axillary temp 101.6⁰F), rest all vitals were stable. There were no signs of any pallor, icterus, clubbing, cyanosis, lymphadenopathy, edema, rash or eschar. Abdominal, respiratory, neurological and cardiovascular system examination were within normal limits.

On evaluation, complete hemogram was suggestive of bicytopenia in which platelets count 80000/mm³, total leukocyte count 2320/mm³ and differential leukocyte count showing neutrophilia (81%). Renal function test, liver function test, urine routine microscopy, electrocardiogram and X ray chest were normal. Topical fever workup which included Widal, Dengue serology, Malaria card test, scrub typhus, Leptospira all were negative. Mantoux test was also done which came out negative. Ultrasonography of the abdomen showed splenomegaly with spleen of approximately 13.3 cm. Blood culture and urine culture report showed no growth after 48 hours of incubation. Patient was empirically started on injection ceftriaxone 1 gram twice daily and tablet doxycycline 100mg twice daily. Over the next 3 days patients hemogram showed a rapid decline in cell counts (on day 3, platelets count was 19,000/mm³ and total leukocyte count was 1180/mm³, ANC 767/mm³).

In view of bicytopenia, bone marrow aspiration and biopsy was done. Bone marrow aspirate smears disclosed mild increase in cellularity (60-80%), with megaloblastic change with maturation arrest in granulopoiesis with increase in histiocytes and occasional histiocytes showing hemophagocytosis (figure 1). Bone marrow biopsy revealed 4-5 ill-defined granulomas (figure 2) comprised mainly of epithelioid cells with increase in histiocytes and monocytoïd cells with occasional histiocytes showing hemophagocytosis. Langhans giant cells or caseation necrosis were absent, ZN stain and PAS stain was negative. Bone marrow aspirate culture was sterile. Typhoid granuloma was therefore speculated because of the fact that there were non caseating bone marrow granulomas with histiocytes showing hemophagocytosis. Extended blood culture was done showed growth of salmonella typhi which further supported typhoid as etiology of bone marrow granuloma in this case.

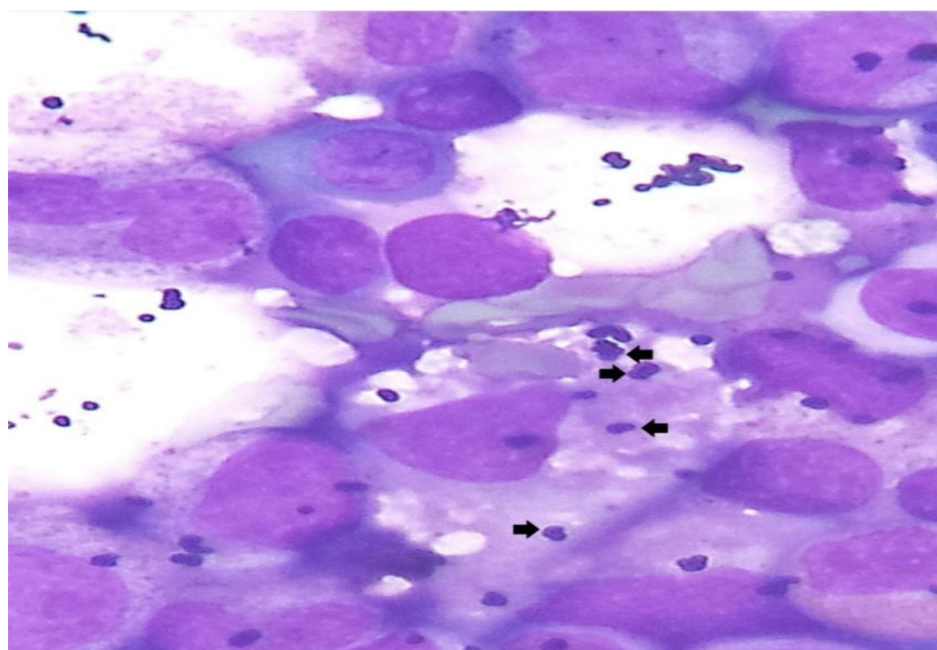


Figure 1. Bone marrow aspirate smear showing a histiocyte exhibiting hemophagocytosis. Wright-Giemsa stained bone marrow aspirate smear at 1000x magnification demonstrating a histiocyte with engulfed red blood cells (black arrows), indicative of hemophagocytosis. No caseating granulomas, giant cells, or necrosis are identified in this field.

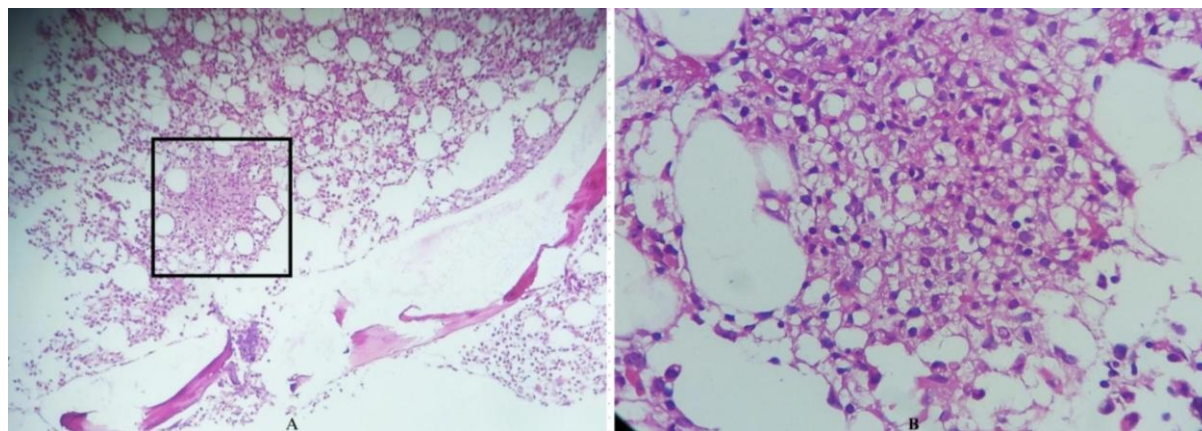


Figure 2. Bone marrow biopsy revealing non-caseating granulomatous inflammation. (A) Low-power view (H&E stain, 10x) of bone marrow biopsy showing focal granulomatous inflammation (outlined in black box) amidst normocellular marrow with preserved pre fat spaces. (B) High-power view (HBE stain, 40x) from the reveals multiple epithelioid histiocytes forming non-caseating granulomas without necrosis or Langhans giant cells. No caseation or fungal elements seen.

Patient's antibiotics were upgraded to injection ceftriaxone 2 gram twice daily for 2 weeks and Tablet Azithromycin 1 gram once daily for 1 week. Patient became afebrile 6 days after initiation of empirical antibiotic therapy and bicytopenia also started improving. At the time of discharge, patient's platelets count was 282,000/mm³ and total leukocyte count was 7300/mm³

Discussion

Granuloma is characterized by localized aggregates of activated macrophages usually with an epithelioid appearance. Lungs are the most common site of granuloma formation but they can be seen in various other parts of body like liver, brain, spleen, bone marrow, skin, lymph nodes, intestine etc. Bone marrow is an unusual site of granuloma formation with an incidence of about 0.3% to 2.2%^[3] with an incidence of only 9.5 cases per year.^[4] Bone marrow granulomas have several possible etiologies, like infectious causes (like tuberculosis, typhoid, brucellosis, Q fever, syphilis, EBV, CMV, etc.) and noninfectious causes like autoimmune, drug-induced, foreign body reaction, and neoplasia.^[5]

Tuberculosis is the most common cause of granulomatous lesion in bone marrow. Regardless of high prevalence of typhoid fever in developing nations, it is still one of the less frequently reported and least striking cause of granuloma formation in bone marrow. Jin et al ^[6] conducted bone marrow biopsy on 49 typhoid patients out of which 8 showed presence of typhoid granuloma. Lee et al ^[7] conducted bone marrow evaluation of about 904 cases out of which 27 showed granulomatous lesions for which tuberculosis was the leading causes 55.5% which was followed by typhoid as etiology of bone marrow granuloma.

Shin et al. ^[8] in his case series described the bone marrow morphology of sixteen patients who had typhoid fever which was confirmed by culture growth of salmonella and categorized them according to the disease stage. Initial 10 days after onset of symptoms was early stage, upto 25 days proliferative stage and beyond that late stage. Granulocytic hyperplasia is the key feature of early stage, hemophagocytosis with ill-defined granuloma in proliferative stage and well-defined granuloma with or without phagocytosis is observed in late stages. Granuloma is seen in only proliferative and late stages of disease and hemophagocytosis is the key feature of typhoid granuloma in bone marrow. Our

patient's bone marrow biopsy showed presence of 4-5 ill-defined granulomas and histocytes showing hemophagocytosis concluding proliferative stage of disease. Muniraj et al^[3] describes a case of 25-year-old male who was suspected to have tuberculosis as etiology underwent bone marrow evaluation which demonstrated epithelioid granulomas with erythrophagocytosis with bone marrow culture showing growth of salmonella.

Granulomatous lesions due to typhoid are reported in various sites of body like liver, spleen, bone marrow, small intestine, mesenteric lymph node, etc. Tiremu et al^[9] reported presence of noncaseating epithelioid granulomas in biopsy of ileum in a blood culture positive typhoid fever patient. Herman et al^[10] described an unusual case of boy aged 10 years who had pain in abdomen for which he underwent Laparoscopic cholecystectomy and his bile culture showed persistent carrier status in spite of the child's negative stool test. The gallbladder histopathology demonstrated a severe granulomatous reaction along with a noticeable thickening of the wall.

Determining whether granuloma formation represents a genuinely rare manifestation of *S. typhi* infection or is merely underrecognized remains difficult. This uncertainty arises from the predominance of typhoid fever in developing regions, where diagnostic resources and reporting may be limited, as well as the scarcity of literature providing detailed morphological descriptions of typhoid associated granulomas.

Conclusion

Therefore, extended blood cultures and bone marrow examination remain indispensable diagnostic tools, particularly in cases with negative routine cultures or persistent clinical suspicion ensuring timely and accurate identification of typhoid fever.

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