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Fibrin-ring granulomas in Scrub typhus: An unrecognized entity

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Abstract- Fibrin-ring granuloma (FRG) is characterized by a ring of fibrin and epithelioid histiocytes arranged around a central fat vacuole. It is classically described in Q fever. We report a case of FRG in the bone marrow biopsy of a 45-year old male with pancytopenia and clinical features of sepsis and bleeding diathesis. Serologically, the antibodies against Orientia tsutsugamushi were positive; being diagnostic of scrub typhus. The patient responded to specific antibiotics and supportive treatment. Thus, scrub typhus should be included as aetiology for FRG.

Index Terms- Fibrin-ring granuloma (FRG); scrub typhus; bone marrow biopsy, sepsis.

I. INTRODUCTION

Fibrin-ring granuloma (FRG) has conventionally been associated with Q fever and is considered to be suggestive of *Coxiella burnetii* infection.[1,2] An epithelioid histiocyte, neutrophil and lymphocytic infiltrate in the shape of a doughnut encasing a vacuole or with an empty central space along with an outer rim, surrounded by eosinophilic fibrinoid material is the composition of FRG.[3,4] Recent literature has thrown light on some other rare causes of FRG in the bone marrow such as viral infections, allopurinol hypersensitivity hepatitis, Hodgkin lymphoma, and peripheral T-cell lymphoma.[5-8] We report a unique case where FRG were noted in a patient with serologically confirmed case of scrub typhus.

II. CASE REPORT

A 45-year old male presented to the casualty with a 12 day history of high-grade fever with chills and rigors and acute epigastric pain. He also had episodes of vomiting and bleeding diathesis in the form of epistaxis and melena since 4 days. On examination, the upper cervical lymph nodes were firm, mobile and moderately enlarged bilaterally. The ultrasound and CT scan showed moderate splenomegaly with mild ascites. The rest of the general and systemic examinations were within normal limits.

The baseline laboratory investigations showed raised blood urea (75 mg/dL) and serum creatinine (2.3mg/dL) levels; indicating mild acute renal failure. The tests for liver profile showed deranged enzymes. The serum amylase level was also elevated (828 units/L).The blood examination were as follows: hemoglobin 5.7 g/dL, total leucocyte count – $2.7x10^3$ cells/ cu.mm., platelets- $14x10^3$ / cu.mm. The peripheral smear confirmed the pancytopenia profile and the differential count showed marked left shift and toxic changes in neutrophils and reactive lymphocytes.

The Quantitative Buffy Coat (QBC) test for malaria and the D-dimer test for hemolysis were negative. The serological tests for HIV-1 and 2, Hepatitis B and Hepatitis C virus were also negative. The coagulation tests showed a mild increase in both PT and APTT. The blood was sent for culture and sensitivity.

A provisional diagnosis of sepsis was considered. Thus, the patient was placed on broad spectrum antibiotics and supportive therapy (platelet transfusion and packed red blood cells). Despite these measures, there was no improvement in the clinical features and cell counts.

In view of the clinical and laboratory findings, a bone marrow study was advised to determine the cause of pancytopenia. The bone marrow aspirate study showed infection associated changes evidenced by an increase in myelopoiesis with toxic changes. An increase in the histiocyte number was also noted. The trephine biopsy showed small, discrete fibrin-ring granulomas consisting of a ring of fibrin arranged around a central fat vacuole. Epithelioid histiocytes were seen around the ring of fibrin (figure 1). No multinucleated giant cells or necrosis were seen. The special stains for mycobacterium tuberculosis and fungal elements were negative.

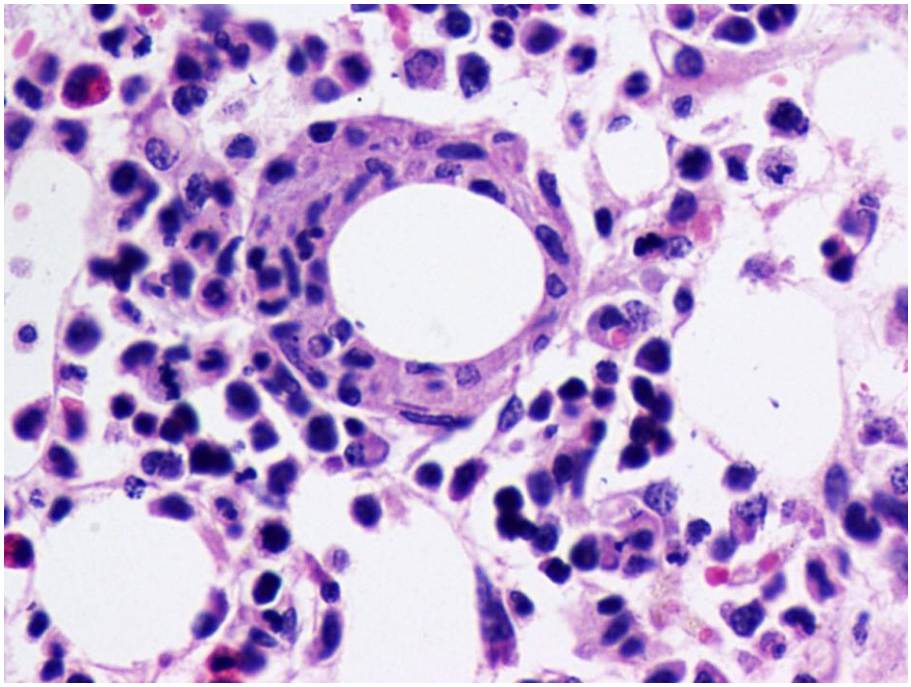

Figure 1: Trephine bone marrow biopsy showing a fibrin-ring granuloma. Prominent eosinophilic fibrinoid material around the doughnut-shaped infiltrate of epithelioid histiocytes and lymphocytes is seen. (Hematoxylin & Eosin ; x200)

Meanwhile, the blood culture study was negative even after 7 days. The serology profile for Q fever, cytomegalovirus and infectious mononucleosis were negative. However, the antibodies against *Orientia tsutsugamushi* were positive; being diagnostic of scrub typhus. The patient was placed on specific antibiotics and supportive treatment and subsequently discharged from the hospital. At the time of submission of this article, the follow up of the patient showed an improvement in the blood counts and clinical features.

III. Discussion

Fibrin-ring granulomas (FRG) are a subset of epithelioid granulomas, possessing distinct microscopic features which aid in their instant identification. They are best described in liver and bone marrow biopsies. It was first described by Bernstein et al in 1965 in a liver biopsy in a diagnosed case of acute Q fever.[9] Bernstein had originally attributed the typical appearance to "eosinophilic necrosis of the sinusoidal walls" as a part of widespread vasculitis in Q fever.

The differential diagnoses of bone marrow granulomas are quite extensive ranging from malignancy and infectious agents to environmental and drug exposure. The infectious aetiology of FRG is widespread. Apart from Q fever, they have been described in Boutonneuse fever (Rickettsia conorii) [10], leishmaniasis, toxoplasmosis and cytomegalovirus infection[5]. Rare associations include hepatitis A virus[11] and Staphylococcus epidermidis.[12] In a recent case study published by Chung HJ and colleagues, Epstein-Barr virus emerged as an important aetiology for FRG. The association is particularly significant in EBV-associated hemophagocytic lymphohistiocytosis and chronic active EBV infection. It also portends a poor prognosis.[13]

The malignancies where FRG are seen include Hodgkin lymphoma and peripheral T-cell lymphoma.[4, 8] Fibrin-ring granulomas have also been described with therapeutic agents such as allopurinol, BCG vaccination and intravesical therapy for carcinoma.[7, 14]

With regard to the morphology of FRG, typically they are small, well-formed granulomas consisting of a ring of fibrin arranged around a central fat vacuole. Epithelioid histiocytes are present around the ring of fibrin. The eosinophilic fibrinoid material can be demonstrated by Masson trichrome stain. More typical granulomas without the fibrin ring generally are present in other areas of the biopsy, which can be overlooked in case of inadequate sections. In atypical cases, the fibrin is intermixed with the histiocytes and does not form a well-defined ring.[15]

IV. Conclusion

Fibrin-ring granulomas are a subset of granulomatous lesions with distinct morphological features, seen in trephine biopsy sections. Although intimately associated with Q fever, the aetiology of FRG is widespread. We report a case of serologically confirmed case of scrub typhus, presenting with pancytopenia and sepsis; showing FRG in the bone marrow. To the best of our knowledge, this is the first reported case of scrub typhus showing FRG in the bone marrow. Thus, scrub typhus should be included in the differential diagnoses of this lesion.

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