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Research Article

BRUCELLOSIS INDUCED ACUTE HEMOLYTIC ANEMIA IN A SEVERE VITAMIN B_{12} DEFICIENT INDIVIDUAL PRESENTING AS PANCYTOPENIA: A CASE REPORT

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A B S T R A C T

Human brucellosis is a common multi-system disease with a wide variety of clinical manifestations. Brucellosis presenting as pancytopenia due to acute hemolytic anemia is rarely reported in literature. Here we report a case of young gentleman who had fever and recurrent jaundice over the last one year, presented with pancytopenia and later diagnosed to have brucellosis induced hemolytic anemia in a vitamin B_{12} deficient individual. Brucella IgM was 15.83 U/ml (positive >12U/ml), however his blood and bone marrow cultures were negative. He was treated with doxycycline and rifampicin for 6 weeks, thereby showing complete resolution of his pancytopenia with no further episodes of hemolysis.

INTRODUCTION

Brucellosis is a common zoonotic infection caused by aerobic intracellular fastidious Gram-negative coccobacilli of the genus Brucella. It is distributed all over the world with endemicity seen in the Mediterranean region and few developing countries. Humans become infected by the ingestion of raw milk, dairy products (especially cheese), and inadequately cooked or raw meat. It is common among veterinary professionals where it is acquired via direct contact with infected animals, products of conception, or animal excreta [1,2].

Brucellosis is a multi-organ involvement disease, however the most common complication is skeletal and joint involvement. It can affect the gastrointestinal system, nervous system, genitourinary system, skin, and respiratory system [3]. Thigh pain is a very characteristic symptom of brucellosis [14]. In the recent years, brucellosis presents predominantly with various hematological manifestations such as anemia, leukopenia, thrombocytopenia, pancytopenia, and rarely as thrombotic microangiopathy [3-6]. The causes of pancytopenia in brucellosis might be due to hemolysis, hemophagocytosis, hypersplenism, bone marrow granulomas, bone marrow hypoplasia, immune mediated destruction, malignant infiltration of bone marrow and nutritional due to vitamin B_{12} and folate deficiency [3,5,6]. Thigh pain is a very characteristic symptom of brucellosis [14] Vitamin B_{12}, or cobalamin, is a water soluble vitamin which after binding intrinsic factor, a glycoprotein produced by the parietal cells in the stomach is absorbed in the terminal ileum. Pernicious anemia is the most common cause of B_{12} deficiency worldwide. Vitamin B_{12} deficiency presents as hemolytic anemia, leukopenia, and thrombocytopenia, macrocytosis, and hypersegmented neutrophils. Vitamin B_{12} deficiency as a cause of hemolytic anemia is extremely (1.5% of cases) [7]. Here we report a case of young gentleman who had fever and recurrent jaundice over the last one year and later diagnosed to have brucellosis induced hemolytic anemia in a vitamin B_{12} deficient individual**.**

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Case Report

A 37 year old gentleman, from Assam, consumes vegetarian diet, farmer by occupation presented to the department of general medicine and personalised health checkup with complaints of generalized weakness, intermittent low grade with on and off for one year. He also stated recurrent episodes of jaundice in the past associated with high-colored urine and vague left-sided abdominal pain and easy satiety. Off late in the last one month he was troubled by a low back ache and multiple large joint pain of no specific character. Over the last 2 weeks he had intense pain in both his thighs. No history of loss of weight, evening rise of temperature, sick contacts or recent travel.

Clinical examination revealed pallor, mild icterus with no palpable lymph nodes. Abdominal examination revealed non-tender splenomegaly 4 cm below the left costal margin. No hepatomegaly. Other system examination was unremarkable. His baseline investigations revealed hemoglobin of 4.4 g/dl. WBC 1500 per microliter, platelet count of 40,000 per microliter. MCV was 118 fl. Total bilirubin 3.7 mg/dl (unconjugated 2.7 mg/dl). AST/ALT 53/34 U/L respectively.

Chest X Ray was normal. Ultrasound abdomen showed splenomegaly (14 cm). Echocardiogram showed no vegetations.

Hemolytic anemia work-up revealed elevated reticulocyte count of 6.2% with markedly raised lactate dehydrogenase 2940 U/L. Peripheral smear showed macrocytosis, hypersegmented neutrophils with polychromasia. Vitamin B_{12} levels were checked and it was < 50 pg/ml. Serum folate and homocysteine levels were normal. Direct and Indirect comb's test were negative. Blood culture showed no growth. Bone marrow examination showed hypercellular marrow with trilineage hematopoiesis with no granulomas. Though vitamin B_{12} deficiency can present as pancytopenia, his other symptoms like arthralgia, thigh pain, low back pain, farmer by occupation made us investigate further for brucellosis despite his negative blood culture and bone marrow examination. Brucella serology was sent and it came positive for Brucella IgM 15.8 (positive >12 U/ml).

He was started on Doxycycline 100 mg twice a day and Rifampicin 450 mg once a day for 6 weeks, along with intramuscular vitamin B_{12} replacement daily for one week followed by oral replacement. He was reviewed in the outpatient department after 6 weeks. He showed remarkable improvement in terms of well-being and constitutional symptoms. His repeat blood counts showed Hb of 8.6 g/dl, WBC 4310 and platelet count of 150000 per microliter with no signs of hemolysis.

DISCUSSION

Brucellosis is a zoonotic infectious disease with multi-system involvement. The global burden of brucellosis remains humongous. It causes more than 500,000 infections per year worldwide. Interest in brucellosis has been increasing because of the growing phenomena of tourism, farming, organic products and migration, in addition to the potential use of Brucella as a biological weapon. [8]

Till date, 8 species have been identified, named primarily for the source animal or features of infection. Of these, the following 4 have moderate-to-significant human pathogenicity: Brucella melitensis (from sheep has the highest pathogenicity), Brucella suis (from pigs) Brucella abortus (from cattle) and Brucella canis (from dogs). The ability of brucellosis to mimic a myriad of infectious diseases and to involve any organ or system in the body had earned it a name "great imitator". Moreover, Brucellosis is often under-diagnosed and under-reported. In addition to all that is said above, in a tuberculosis endemic country like India, an overlap in the clinical presentation has often led to wrong treatment. [9]

Pancytopenia and anemia in brucellosis is explained by a variety of mechanisms of which hemophagocytosis is one of the causes. In a large study of 202 patients, more than 50% of the bone marrow aspirations and biopsies showed features of histiocytic hyperplasia with prominent phagocytosis of erythrocytes, leukocytes, platelets. Another cause being bone marrow granulomas which is usually of non-caseation necrosis type. Hypersplenism can account for cytopenias. However, the enlarged spleen is usually of mild to moderate in size and moreover cytopenias improve before resolution of splenomegaly, and hence it plays a minor role [6].

Bone marrow hypoplasia and malignant infiltration is a rare cause for cytopenias in brucellosis. [6]. Immune mechanisms have also been reported in a few cases [5]. One another rare cause for anemia in brucellosis is due to hemolysis, in the form of microangiopathic hemolytic anemia [10]. A case of acute brucellosis with coombs-positive autoimmune hemolytic anemia had been reported in the literature [5]. However, there has been no case report of brucellosis triggering acute hemolysis in a patient with vitamin B_{12} deficiency. Our patient being a vegetarian, had recurrent episodes of transient jaundice with intermittent fever and joint pains for one year. He was later diagnosed with severe vitamin B_{12} deficiency presenting as acute hemolytic anemia on his initial presentation with brucellosis.

Laboratory findings suggestive of vitamin B_{12} deficiency includes macrocytic anemia, with MCV>115 fl and hypersegmented neutrophils in peripheral smear. Initial evaluation of vitamin B_{12} deficiency is generally a serum vitamin B_{12} levels <200 pg/ml considered suggestive of B_{12} deficiency and levels <100 pg/ml considered severe deficiency. Vitamin B_{12} is an essential cofactor required for DNA/RNA synthesis and fatty acid metabolism. It also plays a vital role in the conversion of homocysteine to methionine. As a result, vitamin B_{12} or folate deficiencies leads to ineffective hematopoiesis and elevated serum homocysteine levels [11]. Intramedullary destruction of red blood cells in vitamin B_{12} deficiency is a well-reported phenomenon, but often not well understood. Moreover, elevated homocysteine levels have been modulated as a possible cause of both intravascular and intramedullary hemolysis with homocysteine increasing hemolysis risk in vitamin B_{12} or folate deficiency [12]. One suggested mechanism being pro-oxidant attributes of homocysteine causing endothelial damage and subsequent microangiopathy [13].

In our case, we found normal homocysteine levels with clear evidence of hemolysis. This suggests other unknown mechanism for this rare entity. Given the low incidence of hemolysis due to vitamin B_{12} deficiency, early suspicion and diagnosis in the appropriate clinical setting is suggested. Further research and newer investigations are warranted for better understanding of the pathophysiology associated with vitamin B_{12} deficiency mediated hemolysis.

CONCLUSION

Brucellosis induced hemolytic anemia due to vitamin B_{12} deficiency presenting as pancytopenia is a rare presentation of Brucella. Unique features of this case report being a young individual who presented with acute hemolytic anemia with pancytopenia and was later diagnosed with profound Vitamin B_{12} deficiency. The investigation did not stop there. His occupation as farmer with splenomegaly, joint pain, especially thigh pain has propelled us to investigate further in the lines of brucellosis. Another interesting feature in this case being, though Brucella IgM was high titers, his blood cultures and bone marrow biopsy were negative for Brucella for unknown reasons. Brucella species could not be established in this case, however his well-being and cytopenias recovered with appropriate antibiotic therapy and nutritional supplementation. High index of suspicion is often required when dealing with scenarios related to pancytopenia as there are mammoth differential diagnosis for this condition.

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