

## Case Report

# Secondary haemophagocytic lymphohistiocytosis in a child with brucellosis

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## ABSTRACT

Human brucellosis is a zoonotic infection, mostly caused by *B. melitensis* and usually presents as an acute febrile illness. Once considered rare in children, it is now recognized that brucellosis can affect persons of all ages, especially in areas where *B. melitensis* is the predominant species. Complications may affect any organ system. On the other hand Secondary Hemophagocytic lymphohistiocytosis (SHLH) can occur due to systemic infections, immunodeficiency, and underlying malignancies. (SHLH) is histologically characterized by excessive proliferation and activation of histiocytes or macrophages. Brucellosis associated with SHLH should be suspected whenever there is a prolonged fever along with hepatosplenomegaly and pancytopenia.

**Keywords:** Brucellosis, Hepatosplenomegaly, Pancytopenia, Secondary haemophagocytic lymphohistiocytosis, Zoonotic

## INTRODUCTION

Human Brucellosis is caused by organisms of genus *Brucella* and continues to be a major health problem worldwide. Although brucellosis is widely recognized as an occupational risk among adults, much of the brucellosis in children is food borne and associated with consumption of unpasteurized milk.<sup>1</sup> Human brucellosis has a wide spectrum of clinical manifestation, including fever, osteoarticular involvement, hepatic, cardiac, central nervous system, or ocular involvement along with hematological abnormalities. On the other hand the childhood histiocytosis constitutes a diverse group of disorders which are frequently severe in their clinical expression. There are two major forms of haemophagocytic lymphohistiocytosis (HLH). The first one is Familial HLH (FHLH), which is an autosomal recessive disorder and the second one is Secondary HLH (SHLH) which is often triggered by infections, auto

immune disorders or malignancy.<sup>2</sup> The pathogenetic mechanisms behind HLH are not completely understood but involve defective granule-mediated cytotoxicity and uncontrolled T-cell activation, leading to an exaggerated inflammatory response.<sup>3</sup>

In this report, authors present this experience with a child with SHLH associated with Brucellosis.

## CASE REPORT

A three and a half year old female child, who was apparently asymptomatic till one month back, was brought to this hospital by her mother with chief complaints of Fever since 1 month, dull activity since 1 month and reduced appetite since 1 month. Fever was insidious in onset, high grade, intermittent, with everyday rise of temperature, not associated with chills and rigors, and subsiding with medication. She had cold and cough

for a very brief period of 2 to 3 days at the onset of fever which subsided with medication. Child also had swelling and pain in the left wrist joint since the onset of fever. There was no history of increased work of breathing, vomiting, altered bowel habits, jaundice, facial puffiness, abdominal distension, headache or bleeding manifestations. There was no significant weight loss. Apparently child did not come in contact with any animals. There was no history of consumption of unpasteurized milk or milk products. The child was second in birth order born to non consanguineous parents with normal birth history. The child was immunized appropriately to the age. Her treatment history records revealed that she was admitted in a private hospital for 15 days prior to admission in this institute, where she was treated with antibiotics with no significant improvement.

At the time of admission in this institute, the child was conscious and coherent, moderately built but sick looking and febrile, axillary temperature measuring 102.0F. Her cardio-respiratory status was stable with respiratory rate of 26 per minute and pulse rate of 128 per minute with normal volume and character. BP was 90/60 mm of Hg. Her weight and height were found on the 50th centile. Significant pallor was noted at the time of admission. There was no significant lymphadenopathy. Abdominal examination showed hepatosplenomegaly. Liver was 5cms below the costal margin and firm in consistency. Spleen was palpable and was grade 2 according to Hacketts classification. The cardio-respiratory and neurological examinations revealed no significant abnormalities.

The initial haemogram showed haemoglobin of 11 gm% with normal leukocyte and platelet counts. Malarial parasite was negative on peripheral smear. ESR was raised with 90 mm at the end of first hour. CRP was raised (>48 mg/L). Dengue serology and Widal tests were negative. Blood and urine samples showed no bacterial growth on cultures. The child's renal parameters, serum electrolytes and chest radiographs were within normal limits. The child was initially treated with broad spectrum antibiotics with supporting fluid therapy for three to four days after admission in this institute. However there was no response to the treatment and the child continued to have high fever spikes.

Suspecting other causes of sepsis and also possibility of SHLH, laboratory workup was again initiated. So haemogram was repeated. As suspected, all the three cell lines were decreased giving a pancytopenic picture with a total WBC count of 3000/cu.mm, platelet count of 80,000/cu.mm and haemoglobin dropping to 7gms%. No abnormal cells were noted in the smear. Serological tests with Weil-Felix test, Leptospiral IgM and Typhi IgM were found to be negative. Her liver function tests revealed elevated enzymes.

However, the Brucella IgM and IgG were both positive showing agglutination to specific antisera. Biochemical

analysis showed raised serum triglyceride levels (510 mg/dl), raised LDH levels (4486 U/L), markedly raised serum ferritin levels (50,000 ng/ml) and low fibrinogen levels (110mg/dl). Bone marrow aspiration cytology revealed phagocytic activity with few large histiocytes. Thus, the diagnosis of Brucellosis with Secondary HLH was confirmed in this child.

With the above clinical background and laboratory evidence, the child was treated with rifampicin (15mg/kg/day) and trimethoprim (10mg/kg/day)-sulfamethaxazole (50mg/kg/day) (TMP-SMX) combination therapy. This is the recommended therapy for children of less than 8 years of age for 6 weeks. The child responded very well to this therapy. Her fever subsided and there was marked clinical improvement within 72 hours after starting the above regimen. Her blood counts became normal after 10 days of treatment.

## DISCUSSION

It's well known that Human Brucellosis, a zoonotic infection affects the host through ingestion of unpasteurized milk or milk products or coming in contact with animals. However several human transmitted infections are also documented and have been published. The first human transmitted infection was documented in 1931.<sup>4</sup> Breastfeeding, aerosolization of involved bacterium, transplacental route and bone marrow transplantation are the commonly reported forms of human transmission.<sup>5-7</sup> In this case, there was no definite history of the child consuming any unpasteurized milk and its products or coming in contact with the animals.

The pathogen, after infecting the host, gets sequestered in the cells of reticuloendothelial system and is known to cause complications involving heart (endocarditis), bone (osteomyelitis), neurobrucellosis and hematological manifestations like anemia, leucopenia, thrombocytopenia and pancytopenia.<sup>8</sup> In the etiopathogenesis of pancytopenia, hypersplenism disseminated intravascular coagulation, hemophagocytosis, bone marrow suppression, destructions in the blood platelets are held responsible.<sup>9</sup>

Hemophagocytic lymphohistiocytosis (HLH) was first defined by Scott in 1939.<sup>10</sup> The mechanisms of hemophagocytosis in non-viral infections may be related to overproduction of activating cytokines, such as TNF- $\alpha$  and  $\gamma$ -interferon, which contribute to macrophage activation, or could be the result of a poorly regulated or inappropriate T-helper lymphocyte response to intracellular pathogens.<sup>11</sup> HLH is characterized by hepatosplenomegaly, bicytopenia, hypertriglyceridaemia, hyperfibrinemia and high level of liver function tests and lactate dehydrogenase (LDH).<sup>12</sup>

The findings of brucellosis, including pancytopenia, fever, and splenomegaly were also among the main clinical features in HLH.

Although literature review shows that many authors recommend IVIG and other agents like etoposide, cyclosporine A and corticosteroids for treating the SHLH along with antibiotic therapy, but in this case the child responded to the specific antibiotic therapy alone, targeting brucella organism i.e. with rifampicin and co-trimoxazole combination therapy which is recommended for children of less than 8 years of age. Karakulukcu et al. described four children with Brucella-associated HLH.<sup>13</sup> The authors reported that all of four patients had pancytopenia and recovered fully with specific antimicrobial therapy for Brucella infections. Similarly El-Amin et al also reported cure rate of 90% with combination of rifampicin and co-trimoxazole for 6 weeks.<sup>14,15</sup>

## CONCLUSION

Children who are diagnosed with brucellosis and associated with high fever, hepatosplenomegaly and pancytopenia, possibility of SHLH should be considered and evaluated. Treating the underlying cause of SHLH is of utmost importance and therapeutic agents' specific to SHLH should be considered in life threatening situation.

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