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FATAL HAEMOPHAGOCYTIC SYNDROME AND HEPATITIS ASSOCIATED WITH VISCERAL LEISHMANIASIS

P Mathur, *JC Samantaray, P Samanta

Abstract

Haemophagocytic syndrome (HPS) secondary to infections occurs due to excessive, non-malignant proliferation of histiocytes, with resultant haemophagocytosis. The syndrome is essentially treatable, provided timely etiological diagnosis is achieved. In this report, we present a rare case of a child who hailed from Uttaranchal and presented with severe hepatitis. Bone marrow examination revealed an unexpected diagnosis of HPS secondary to visceral leishmaniasis. Despite initiating appropriate antileishmanial treatment, the child had a fatal outcome.

Key words: Fatal, haemophagocytic syndrome, hepatitis, visceral leishmaniasis

Visceral leishmaniasis (VL, kala-azar) is a systemic infection of the reticuloendothelial system caused by protozoa of the genus Leishmania. Haemophagocytic syndrome (HPS) is a potentially fatal condition characterized by excessive proliferation and activation of histiocytes with resultant phagocytosis of blood elements (haemophagocytosis).1,2 There is an overlap in the clinical presentations of VL and HPS, both of which present with fever, hepatosplenomegaly and pancytopenia. However, VL patients consistently have marked hypergammaglobulinaemia and the patients of HPS have haemophagocytes in the marrow with or without coagulopathies. HPS can occur as primary (familial) lymphohistiocytosis or secondary forms, due to neoplasms, collagen vascular diseases or infections.2 The most common infectious causes of HPS are viral infections like Epstein–Barr and other members of Herpes virus family and bacterial sepsis.3 HPS secondary to VL is extremely rare and due to overlapping clinical features, may be missed if a diligent screening of bone marrow is not performed. We report a rare, fatal case of VL-associated HPS, who also had extreme derangement of liver functions.

Case Report

A four-year-old child from the hilly areas of Uttaranchal state of India presented with fever since 4 months, along with abdominal pain and jaundice since 1 month. The patient was investigated at his native place; however, no cause could be ascertained for his fever. He was then referred to a private nursing home in Delhi, where he remained admitted for 15 days. A thorough laboratory investigation, including a bone marrow examination was performed there, which again failed to clinch any diagnosis. He started developing high-grade fever and jaundice and was therefore referred to our hospital, which is a tertiary care center of northern India. At the time of admission to our hospital, the child was febrile, had toxic appearance, marked icterus, black facial pigmentation, splenomegaly (7 cm below left costal margin) and hepatomegaly (11 cm below right costal margin). His respiratory and cardiovascular systems were within normal limits.

Laboratory investigations at the time of admission revealed pancytopenia (haemoglobin 9 g/dL, leucocyte count 2600/mm³ and platelets 45,000/mm³), hypergammaglobulinaemia and hypoalbuminaemia (total protein 5.9 g/dL, albumin 2.1 g/dL and globulin 3.8 g/dL). The patient had deranged liver functions (serum bilirubin 5.8 mg%, aspartate transaminase 4200 IU/mL, alanine transaminase 8900 IU/mL, alkaline phosphatase 300 IU). His kidney function tests were within normal limits. A set of blood and urine cultures were sterile and peripheral smears were negative for malarial parasite. The patient was also found to be negative for antibodies to HIV, hepatitis A, E and C viruses and typhoid and dengue fever. The hepatitis B surface (HBsAg) and e (HBeAg) antigens were also negative. The X-ray of chest was normal at the time of admission, however, ultrasonography of abdomen revealed diffuse hepatosplenomegaly without any focal lesions. A bone marrow aspiration was done to rule out malignancy. However, examination of a Giemsa stained bone marrow aspirate revealed numerous histiocytes, Leishman Donovan (LD) bodies (Fig. 1, inset A and Fig. 2) and haemophagocytes (Fig.1, inset B and Fig. 3). An immunochromatographic test for antibodies to rK 39 antigen of Leishmania donovani (Kala-azar Detect, In Bios, USA) was also positive.

The child was treated with sodium stibogluconate (20 mg/kg) for 5 days. However, there was no response and the treatment was switched to amphotericin B (1 mg/kg/day). In spite of this, his condition deteriorated and he started showing signs of respiratory distress along with bleeding from nose and mouth on the second day of...
amphotericin therapy. An X-ray of chest showed bilateral infiltrates at this time. The prothrombin time was found to be 14/23′′ and platelet count was 13,000/mm$^3$. Despite supportive measures in the form of blood transfusion, mechanical ventilation and broad spectrum antibiotics, his condition deteriorated and the child expired due to disseminated intravascular coagulation.

Discussion

Haemophagocytic syndrome due to kala-azar is a rare entity with only around 30 cases reported in English literature till date.$^1$-9 In a review of all the published cases of HPS associated with VL in English literature, we found that almost all of them were cured following treatment. In the present case, there was a prolonged delay in the initiation of treatment due to its failure to be diagnosed as a case of VL at his native place. By the time the patient was referred to us, his marrow had numerous histiocytes showing haemophagocytosis. The patient hailed from a mountainous region, non-endemic for VL in India. Since the pathognomonic features of kala-azar like fever with hepatosplenomegaly and pancytopenia can also be found in other infections like typhoid, malaria and tuberculosis or malignancies prevalent in our country, unsuspecting clinicians can miss a diagnosis of VL in non-endemic areas. In tropical countries like India, a thorough search should be made for the various causes of prolonged fever in order to initiate timely and appropriate treatment.

Although minor derangements of liver functions have been observed in patients of VL,$^10$ severe hepatitis as a presenting feature is extremely rare. The patient in this report had marked icterus and transaminases at the time of presentation, which may have contributed to his fatal outcome, since severe hepatitis is a poor prognostic marker in cases of VL.

The various infectious agents incriminated in the pathogenesis of haemophagocytosis stimulate the immune system, resulting in the activation of T lymphocytes. The T lymphocytes in turn produce cytokines, which stimulate proliferation and activation of histiocytes.$^3$ The type of HPS is important in determining the most effective treatment. For primary HPS, bone marrow transplantation and cytotoxic therapy is the treatment of choice; whereas in secondary forms, specific treatment of underlying illness with or without steroids can cure the patients.$^4$ Since *Leishmania* amastigotes themselves parasitize the macrophage-monocyte lineage of cells, there is already gross pancytopenia and cytokine imbalance. This cytokine imbalance may predispose the patients of VL to HPS.$^4$ In patients of HPS secondary to VL-associated HPS, amphotericin B, along with a short
course of corticosteroids is recommended when signs of HPS predominate.\textsuperscript{4} Our patient was initially administered sodium stibogluconate as is the protocol for treatment of VL at our hospital. When there was no response, the treatment was changed to amphotericin B. This delay may also be a contributory factor for the fatal outcome. In the remote, backward areas of tropical countries, where infections predominate, expert bone marrow microscopic facilities are rarely available. In such circumstances, probably, many more cases of reactive haemophagocytosis may be going undetected and perhaps also contributing to the bulk of unexplained mortality due to infectious diseases. Therefore, in patients diagnosed as having HPS, an urgent screening for etiological agents should be done in order to initiate aggressive and effective treatment.

References


