CASE REPORT

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Hemophagocytic Lymphohistiocytosis (HLH) complicating the double trouble of Malaria and Kala-azar - a rare presentation

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare hyper-inflammatory syndrome which is characterized by inappropriate proliferation of lympho-histiocytes which phagocytize hematopoietic cells and thereby give rise to the clinical picture of fever, hepatosplenomegaly and cytopenias. HLH can be primary or secondary due to infections by bacteria, viruses, parasites and fungi. Here we present a case report of simultaneous infection of *Plasmodium vivax* and visceral leishmaniasis complicated by secondary HLH in a Border Security Force jawan (BSF soldier).

Key words

Fever, hemophagocytic lymphohistiocytosis (HLH), Hepatosplenomegaly, kala-azar, malaria.

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Background

Indian subcontinent is home to a lot of vector borne diseases. Malaria is the most common vector borne illness in India accounting for more than 3/4th of the cases reported from Southeast Asia. It occurs mostly in young adults in their productive years leading to a loss of disability adjusted life years and hence has grave economic consequences. It is caused by Plasmodium species spread by mosquito bite. Malarial infection by *P. vivax* and *P. falciparum* may lead to systemic inflammatory response and multi-organ failure [1]. Visceral leishmaniasis or kala-azar as it is commonly known, is a vector borne illness which affects the bone marrow liver and spleen. It is caused by *Leishmania donovanii* which is spread by female Phlebotomus sand fly. India accounts for two thirds of the global burden of kala-azar [2]. It is not rare to find infection with both in the same individual at the same time, especially in endemic regions resulting in various complications [3]. HLH is a multi-system inflammatory response caused by excessive stimulation of antigen presenting cells. Secondary HLH complicates many viral and parasitic illnesses. There has been no report of HLH complicating the double infection of malaria and kala-azar. Here we present a rare case of infection with both the parasites which was complicated by the development of HLH.

Case Report

A 31 year old BSF soldier, native of district Dumka, Jharkhand, India, with recent visit to his native place presented to BSF base hospital with chief complaints of high grade fever associated with chills and rigors of 2 days duration. There was no history of cough with expectoration, burning micturition, skin eruptions, altered sensorium, headache or vomiting. His peripheral blood film examination showed trophozoites of *P. vivax*. He was started on standard anti-malarial treatment with chloroquine and primaquine. Even after completing the course of chloroquine he continued to remain febrile with a temperature of around 103^{o}F on most of the occasions. On the fourth day he suddenly had an episode of epistaxis. This prompted a complete blood count which revealed anemia, thrombocytopenia and leucopenia. He was then referred to Government Medical College and Hospital, Amritsar in view of persisting fever and low blood counts.

He presented to us in the outpatient department with chief complaint of fever. Physical examination revealed a blood pressure of 124/78 mm Hg, pulse rate of 96/min, respiratory rate of 20/min and a temperature of 103^{o}F. There was moderate amount of pallor, no icterus, no cyanosis, no clubbing, no lymphadenopathy and no peripheral edema. Liver was palpable with a span of 16cm, was soft in consistency and non-tender. Spleen was also palpable 9 cm below costal margin. His initial blood investigations showed a hemoglobin 10.7g/dL, total leukocyte count (TLC) 1800/mm^3, platelet count 43,000/mm^3, serum bilirubin 0.9mg/dL, aspartate transaminase 31U/L, alanine transaminase 26 U/L, lactate dehydrogenase 275 U/L, total serum protein 8.5 g/dL, serum albumin 3.2 g/dL and blood urea 26 mg/dL. Patient was not found to be glucose-6-phosphatase deficient. Patient was started on injectable antibiotics and artesunate and was followed up with blood counts. Blood investigations on day ten revealed Hb of 6.8 g/dL, TLC of 2100/mm^3 and platelet count of 30,000/mm^3. Urine and blood cultures were sterile. Inspite of receiving full course of anti-malarials patient continued to be febrile. As he belonged to kala-azar endemic regions of India, a rapid card test (testing rK39 antigen) and a leishmania antibody was done and both of which came out to be positive. Bone marrow examination was done which revealed a picture of hemophagocytic syndrome with many macrophages showing engulfed platelets, leucocytes and RBCs (Figure-1).

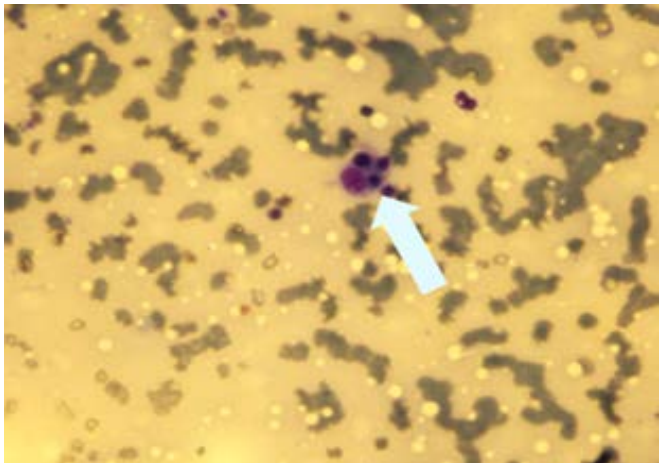

Figure 1 - Bone marrow examination showing a macrophage with engulfed leucocytes

He was started on sodium stibogluconate at a dose of 20mg/kg/day intramuscular for 28 days. He continued to be febrile and his hemoglobin had fallen to 6.8g/dL, TLC was 2900/mm^3 and platelets were 50,000/mm^3. Serum ferritin was increased (4257 ng/ml).

Applying the Histiocyte Society, 2004 criteria a possibility of secondary HLH was kept and the patient was started on injectable dexamethasone. After 5 days of starting the steroids blood counts started improving with an Hb of 8.0g/dL, TLC of 3900/mm^3 and platelet count of 140,000/mm^3 and the patient became afebrile. Injectable steroids were continued for another week after which they were slowly tapered and stopped. He was discharged with an Hb of 11.2 g/dL, TLC 6500 /mm^3 and a platelet count of 160,000/mm^3.

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Discussion

Hemophagocytic lymphohistiocytosis

HLH is a life threatening hyper-inflammatory consequence of many underlying conditions and can affect any age group [4]. HLH was earlier thought to be a sporadic disease caused by proliferation of histiocytes. Afterwards a familial variety of HLH was described. However, in 1965 simultaneous development of fatal HLH in a father and his son was reported which suggested that infection could be the underlying etiology [5]. Non-familial variety of HLH is a consequence of a rampant inflammatory response to an infective agent in most cases [6]. Incessant stimulation of histiocytes and lymphocytes leads to excessive production of cytokines which result in the peculiar symptoms of HLH, namely fever, hepatosplenomegaly, cytopenias and hemophagocytosis [5]. Hemophagocytosis is a pathological finding of activated macrophages, engulfing erythrocytes, leucocytes, platelets, and their precursor cells and thereby leading to cytopenias [7]. The syndrome occurs due to defective cytotoxic activity of natural killer (NK) cells and cytotoxic T-lymphocytes which become excessive and uncontrolled with ineffective clearance of antigen along with excessive aggregation of activated T lymphocytes, histiocytes and macrophages in response to infective stimulus [8].

Etiology

HLH can be primary or secondary. Primary HLH which is a familial erythrophagocytic lymphohistiocytosis is an autosomal recessive disorder with various genetic mutations and is generally seen in childhood and infancy. It can be a part of immune deficiency syndrome. Secondary HLH occurs after immunological activation following systemic infection, immunological deficiency or due to an underlying malignancy. Amongst the infectious causes of HLH viral infections mainly Epstein-Barr virus (EBV), Cytomegalovirus (CMV), measles, adenovirus are pre-dominant pathogens [9]. Other infections include Gram negative bacteria, tuberculosis, malaria, leishmania, leptospira, brucella and fungal infections. There have been few case reports of HLH complicating leishmaniasis [10-16] and HLH complicating *P. vivax* [17-19]. Double infection with leishmaniasis and *P. vivax* complicated by HLH has not been reported in literature though a double infection with leishmaniasis and EBV has been reported which prompted this case report [20].

Diagnostic dilemma

Our case presented with fever, hepatosplenomegaly and pancytopenia with peripheral blood smear suggestive of *P. vivax* malaria and failure to improve with therapy prompted us to further investigate the patient. He was simultaneously harboring an infection with leishmania as well, diagnosis of which would have been a rare possibility in northern India. History of his stay at Jharkhand (which is an endemic region of kala-azar) made us suspect and investigate for the same. There was evidence of hemophagocytosis on bone marrow examination (Figure 1) and hyper-ferritinemia. The patient fulfilled the diagnostic criteria (Table 1) laid down by Histiocyte Society's HLH study group [20].

Table 1. HLH diagnostic criteria, 2009[19]

1. Molecular diagnosis of hemophagocytic lymphohistiocytosis (HLH) or X-linked lymphoproliferative syndrome (XLP).
2. Or at least 3 of 4:
a. Fever
b. Splenomegaly
c. Cytopenias (minimum 2 cell lines reduced)
d. Hepatitis
3. And at least 1 of 4:
a. Hemophagocytosis
b. Raised Ferritin
c. Raised sIL2R* (age based)
d. Absent or very decreased NK function
4. Other results supportive of HLH diagnosis:
a. Hypertriglyceridemia
b. Hypofibrinogenemia
c. Hyponatremia

*Soluble interleukin 2 receptor

Even after giving full treatment with anti-malarials and anti-leishmanial agent patient's blood counts continued to fall. So to check the uncontrolled hyperinflammatory state corticosteroids were started. After five days of starting the corticosteroids patient's counts started rising and the fever subsided. In most of the cases treatment of the inciting cause is sufficient and aborts the hyper-inflammatory state but rarely there may be need of immune-suppressive therapy as in our case [9, 21].

Conclusion

This case report is to highlight the fact that double infection with *P. vivax* and leishmania although rare in endemic regions and in the setting of unresolving fever, cytopenias and hepatosplenomegaly even after a proper course of anti-microbials, a possibility of HLH should be considered. If left unrecognized and untreated, it can be fatal.

Abbreviations

Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Hemophagocytic lymphohistiocytosis (HLH), natural killer (NK) cells, total leukocyte count (TLC).

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Competing interests

None declared.

Authors' contribution

The first four authors were the consultant physicians of the patient and helped reach the diagnosis along with the help of the Microbiologist Deepshikha Mangat. Dr. Smit Rajput was attending postgraduate who was involved in patient care.

Authors' information

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