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VISCERAL LEISHMANIASIS UNVEILING AS HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS – INSIGHTS FROM TWO NON-ENDEMIC CASES WITH VARIED PRESENTATION

General Medicine

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ABSTRACT

Visceral leishmaniasis-associated hemophagocytic lymphohistiocytosis (VL-HLH) is a potentially life-threatening condition caused by an overactive immune response triggered by protozoan parasites belonging to the Leishmania species and transmitted by infected sandflies. Given the similarities between the clinical presentation of visceral leishmaniasis and hemophagocytic lymphohistiocytosis, identifying leishmaniasis as the underlying disease demands heightened clinical suspicion. The occurrence of secondary HLH has a great impact on prognosis. VL-HLH incidence is increasing in non-endemic areas where the disease is severe, and mortality rates are high. We report two cases of VL-HLH, presenting at a tertiary care centre in the foothills of Himalaya highlighting the variability in clinical presentation and outcomes despite sharing the same underlying disease. The first case involved a patient with no notable medical history, presenting with persistent fever, abdominal pain, and significant weight loss. The second case featured a patient with untreated thyroid carcinoma, exhibiting prolonged fever and an abrupt onset of altered mental state without prior neurological symptoms. Although both cases were ultimately diagnosed with VL-HLH, their clinical trajectories differed significantly, illustrating the unpredictable nature of this condition. The varied presentations and outcomes of these two cases underline the necessity for healthcare providers to maintain a high index of suspicion for VL-HLH, facilitating early diagnosis and timely intervention to improve patient prognoses.

KEYWORDS

leishmaniasis, hemophagocytic lymphohistiocytosis, , persistent fever

INTRODUCTION

Visceral leishmaniasis (VL), also known as kala-azar, is a systemic disease caused by the protozoan parasites of the Leishmania genus, transmitted by the bite of infected female phlebotomine sandflies. This disease is predominantly found in areas close to water bodies, which serve as breeding grounds for the sandfly vector, making low-altitude riverine environments particularly vulnerable. Despite traditionally being endemic to the eastern states of India such as Bihar, West Bengal, Jharkhand, and Uttar Pradesh, there has been an epidemiological shift with new cases emerging from the sub-Himalayan region of Uttarakhand, an area not previously known for VL [1,2,3]. These shifts in disease distribution underscore the evolving nature of VL's epidemiology. Unique to the region, VL primarily presents in its visceral form rather than as cutaneous leishmaniasis, often co-occurring with hemophagocytic lymphohistiocytosis (HLH) syndrome [4].

HLH is a syndrome of excessive immune activation characterized by widespread inflammation and tissue damage due to an overactive immune response [5]. This condition can manifest in two forms: primary (genetic) HLH, which is typically observed in children and progresses rapidly, and secondary (acquired) HLH, which can occur in the context of infections, autoimmune diseases, or malignancies [6,7,8]. Notably, both forms of HLH can be precipitated by infectious agents or other immunological stimuli, with some patients displaying genetic predispositions regardless of age or familial history.

Diagnosis of HLH relies on a combination of clinical signs, laboratory findings, and, in some cases, genetic testing, adhering to criteria set forth by the Histiocyte Society. [Table 1] A diagnosis may be considered in the absence of genetic evidence if a patient meets five of the eight specified criteria [9].

Given the life-threatening nature of HLH and the potential for its occurrence alongside VL, especially in light of geographical shifts in VL endemicity, there is a critical need for increased awareness and prompt diagnosis. Understanding the interplay between VL and HLH, particularly in emerging regions of incidence, is essential for timely and effective intervention, ultimately aiming to reduce morbidity and mortality associated with these conditions.

Table 1- Criteria For Diagnosis Of Hemophagocytic Lymphohistiocytosis

A. Molecular diagnosis compatible with hemophagocytic lymphohistiocytosis
OR
B. At least five out of the eight following criteria:
1. Fever
2. Splenomegaly
3. Cytopenias (two or more lineages)
- Hemoglobin <9g/dL or <10g/dL in newborn babies
- Platelets <100 X 10^9/L
- Neutrophils <1.0 X 10^9/L
4. Hypertriglyceridemia (>265 mg/dL) or hypofibrinogenemia (<150mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph nodes or liver without any evidence of malignancy
6. Decreased or absent activity of natural killer cells
7. Serum Ferritin >500 µg/L
8. Increased soluble CD25 (>2400 U/ml)

Case Presentations:

Case 1:

A 32-year-old male, from the Ganga belt region, with no prior comorbidities, a reformed smoker and occasional alcohol consumer, presented with a three-month history of fever which was high-grade, more intense in the evening, accompanied by chills and rigors, and did not subside with medication. He also reported abdominal pain for the past month, characterized as diffuse, dull aching pain, localized to the left upper quadrant with dragging sensation, associated with anorexia and significant weight loss. He denied experiencing nausea, vomiting, diarrhoea, constipation, shortness of breath, chest pain, or dysuria. On examination, his vitals were stable, but he exhibited pallor and hepatosplenomegaly. Laboratory investigations revealed pancytopenia and deranged liver function tests and an elevated INR. He tested negative for HIV, hepatitis B, and hepatitis C. [Table 2] He had markedly elevated serum ferritin levels and elevated serum lactate dehydrogenase (LDH). Both direct and indirect Coombs tests were negative. Investigations for common causes of tropical fever were negative. Given the constellation of fever, pancytopenia, hepatosplenomegaly, high serum ferritin, and hypertriglyceridemia, he was suspected of having hemophagocytic lymphohistiocytosis (HLH) and was further evaluated. Bone marrow aspiration revealed hemophagocytes, [Figure 1A] and the biopsy showed a hypercellular marrow with erythroid and megakaryocytic hyperplasia. Serological testing for visceral leishmaniasis returned positive with the RK-39 test, although no Leishman-Donovan (LD) bodies were observed in the bone marrow examination. The diagnosis of visceral leishmaniasis-induced secondary HLH led to the initiation of intravenous liposomal amphotericin B. The patient demonstrated significant improvement; fever spikes and pancytopenia resolved, and his spleen size decreased.

He reported feeling better overall and received a total of 5 doses of intravenous liposomal amphotericin B, with renal and liver function tests monitored closely. He was discharged in a hemodynamically stable condition, with instructions to return for the sixth and seventh doses of liposomal amphotericin B. Follow-up visits revealed further clinical improvement and a reduction in spleen size from 8 cm to 4.5 cm below the costal margin.

Case 2:

A 42-year-old male from Uttarakhand, with a history of biopsy-proven, untreated carcinoma of the thyroid, presented to emergency with a three-month history of intermittent high-grade fever associated with chills and rigors, but without an evening rise in temperature or night sweats. Additionally, he experienced hypoactive delirium for two days without any history of loss of consciousness, seizures, abnormal body movements, meningeal signs, or head trauma. On examination, he exhibited low blood pressure requiring ionotropic support, along with pallor, thyroid gland swelling, and splenomegaly. Laboratory tests revealed pancytopenia and deranged liver function tests including hypergammaglobulinemia [Table 2]. Serology for HIV, hepatitis B and hepatitis C were all negative. All tests for common causes of tropical fever were negative, but the RK39 test for leishmaniasis was positive. Given the combination of fever, pancytopenia, splenomegaly, he was suspected of having hemophagocytic lymphohistiocytosis (HLH) and was further evaluated. Further investigations revealed high ferritin levels, and hypertriglyceridemia, bone marrow aspiration and biopsy, confirmed the presence of Leishman-Donovan (LD) bodies and hemophagocytes, leading to a diagnosis of visceral leishmaniasis-induced secondary HLH. He was initiated on intravenous liposomal amphotericin B treatment. Despite these interventions, he developed multiple complications indicative of advanced systemic involvement. His fever persisted while his ionotropic requirement increased. Laboratory indicators revealed worsening pancytopenia, with a notable decrease in platelet count and hemoglobin levels. He began to show signs of acute renal failure and liver failure. He was transferred to the intensive care unit, where his respiratory function began to fail necessitating mechanical ventilation. Despite aggressive resuscitative efforts, he succumbed to refractory septic shock and multiorgan failure.

Table 2: Baseline Investigations

Laboratory data	CASE 1	CASE 2
Hemoglobin (g/dl)	7	5.1
White blood cell count (/mm^3)	2300	1100
Neutrophil (/mm^3)	1216	680
Platelet count (/mm^3)	60000	12000
International normalized ratio (INR)	1.08	2.46
Blood Urea (mg/dL)	23	34
S. Creatinine (mg/dL)	0.9	1.0
Total calcium (mg/dL)	8.9	9.0
Total Bilirubin (mg/dL)	1.07	0.77
Alanine transaminase, units per liter (ALT, U/L)	288	138
Aspartate transaminase, units per liter (ALT, U/L)	176	304
Alkaline phosphatase, units per liter (ALP, U/L)	702	691
Gamma glutamyl transferase, units per liter (GGT, U/L)	300	159
Serum Albumin (g/dL)	2.56	1.82
Serum globulin (g/dL)	2.69	4.31
Triglycerides (mg/dL)	271	304
Serum ferritin (ng/mL)	7223	5438
Lactate dehydrogenase, units per liter (LDH, U/L)	1308	1232
Fibrinogen	259	156
Viral markers	Non reactive	Non reactive
RK 39	+	+
Bone marrow aspiration and biopsy	Hemophagocytes +, LD bodies -	Hemophagocytes +, LD bodies +

Differential Diagnosis

Given the constellation of symptoms—fever, splenomegaly, pancytopenia, elevated serum ferritin, and liver function abnormalities—several conditions parallel the clinical presentation of our cases, necessitating a broad differential diagnosis. The primary conditions to consider include infectious diseases like malaria, dengue, and other endemic fevers, which are prevalent in similar geographic regions and can mimic the haematological and systemic manifestations of visceral leishmaniasis (VL) and hemophagocytic lymphohistiocytosis (HLH). Lymphoproliferative disorders, including lymphomas and leukemias, are crucial in the differential diagnosis. The presence of an underlying untreated carcinoma in one of the patients further complicates the clinical picture, necessitating the exclusion of malignancy-associated HLH (MAHS). Infectious diseases such as tuberculosis (TB) and HIV, which are endemic in several regions including the foothills of the Himalayas, should also be considered. These infections can cause similar clinical presentations and have been known to trigger secondary HLH. Thus, appropriate testing for TB, HIV, and other opportunistic infections is warranted. Lastly, other causes of fever of unknown origin (FUO), including endemic fungal infections and other parasitic diseases, should be explored.

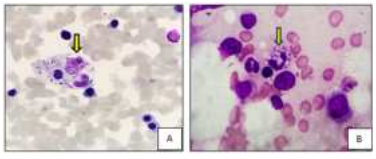

Figure 1: (A) Bone marrow aspirate from case 1 showing prominent hemophagocyte. (B) Bone marrow aspirate from case 2 showing extracellular and intracellular Leishmania Donovan bodies.

DISCUSSION

In this article, we delve into two distinct manifestations of visceral leishmaniasis (VL) evolving into hemophagocytic lymphohistiocytosis (HLH), highlighting the diverse clinical spectrum and the diagnostic as well as therapeutic challenges posed by this association. Both patients hailed from areas not traditionally endemic for VL, reflecting the geographic spread of this disease and the critical importance of considering VL in the differential diagnosis for HLH, particularly in the presence of fever, splenomegaly, and cytopenias.

The first case illustrated a patient with unremarkable medical history presenting with classical symptoms of VL alongside signs suggestive of HLH, leading to a diagnosis based on serology and bone marrow findings. The second case involved a more complex presentation with an underlying untreated carcinoma, exhibiting both VL and HLH symptoms, complicating the clinical picture and ultimately leading to a fatal outcome. These cases underscore the pivotal role of comprehensive and multimodal diagnostic strategies. Serological testing for VL, including the rK39 antigen test, coupled with confirmatory evidence from bone marrow aspiration, showcases the critical steps in clinching the diagnosis (10). This process emphasizes not just the biological underpinnings of VL and HLH but also the importance of a methodical approach to unravelling complex cases where initial presentations might mask the underlying etiology.

The management of VL-HLH involves addressing the underlying infection with anti-leishmanial therapy while concurrently mitigating the hyperinflammatory state intrinsic to HLH. This therapeutic strategy underscores the complexity of managing cases where infectious etiologies trigger secondary immune dysregulation syndromes. The treatment approach in our cases, particularly the use of liposomal amphotericin B, aligns with current recommendations and highlights the importance of an integrated approach to managing this complex condition (11). However, the challenges in diagnosing and managing HLH in the context of VL, as highlighted by the contrasting outcomes in our cases, demonstrate the critical need for early diagnosis and initiation of treatment.

In conclusion, our cases contribute to the growing body of evidence on the association between VL and HLH, emphasizing the variability in clinical presentations and outcomes. They highlight the importance of considering VL in the differential diagnosis of HLH, particularly in regions where VL is emerging or not traditionally endemic. Early recognition, accurate diagnosis, and prompt treatment initiation can significantly alter the course of the disease. The evolving epidemiological landscape of VL, coupled with the life-threatening potential of secondary HLH, demands an integrated approach to patient care, encompassing awareness, timely diagnosis, and appropriate management strategies.

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