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Leishmania induced Hemophagocytic Lymphohistiocytosis (HLH) syndrome in a patient with Systemic Lupus Erythematosus (SLE)

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Abstract

This case report describes a challenging diagnostic journey of a young woman with a history of hypothyroidism and Systemic Lupus Erythematosus (SLE), presenting with a three-month fever, abdominal pain, and pancytopenia. Initial suspicion of SLE with Macrophage Activation Syndrome (MAS) led to methylprednisolone pulse therapy, providing transient relief. Further assessment revealed dark brown macules, edema, ascites, and splenomegaly. Laboratory findings showed elevated ferritin, triglycerides, and decreased fibrinogen. Negative SLE flare markers prompted investigation for visceral leishmaniasis, supported by a positive rk39 test, LD bodies in bone marrow, and hemophagocytes. The conclusive diagnosis was visceral leishmaniasis-associated Hemophagocytic Lymphohistiocytosis (HLH). The patient received intravenous immunoglobulin and liposomal amphotericin B, achieving fever resolution. This case emphasizes the importance of considering unusual etiologies in complex presentations, particularly in endemic regions, showcasing the intersection of autoimmune and infectious diseases. Prompt diagnosis and appropriate management are crucial in improving outcomes in such complex presentations.

Keywords: Leishmaniasis; Hemophagocytic lymphohistiocytosis; Pancytopenia.

Introduction

Leishmaniasis is caused by an obligate intracellular parasite, and 21 pathogenic Leishmania species have been identified [1]. Today, more than one billion people live in areas where leishmaniasis is endemic and are susceptible to infection. An estimated 30,000 new cases of VL and over 1 million new cases of CL occur annually on a global scale in 2020, with 18% of the global burden of kala-azar borne by India. Since the beginning of intensified efforts in 1992 (77,102 cases), kala-azar cases have decreased by 98% (1275 cases in 2021) [2].

Leishmaniasis can present in three distinct clinical manifestations, namely cutaneous, mucosal, and visceral forms. Secondary Hemophagocytic Lymphohistiocytosis (HLH) syndrome can occur in around 1% of cases of leishmaniasis.

Hemophagocytic Lymphohistiocytosis (HLH) has the potential to manifest across all age cohorts, resulting in mortality in around 80% of instances. Bacterial and viral infections, as well as malignancies such as HLH syndrome, are the prevailing causative factors [3].

The term "Macrophage-Activation Syndrome" (MAS) refers to hypercytokinemia brought on by autoimmune/autoinflammatory disorders.

The precise mechanisms behind the development of Hemophagocytic Lymphohistiocytosis (HLH) as a result of leishmaniasis remain uncertain. The defective regulation of infections results in the hyperactivation of macrophages or histiocytes by the parasites, leading to a failure in the recognition of normal and undamaged blood cells [4].

In this report, we describe a clinical case involving a young female patient diagnosed with Systemic Lupus Erythematosus (SLE) and hypothyroidism. The patient arrived with symptoms of chills and a high-grade fever. The patient had been previously hospitalised due to abdominal distension and pancytopenia, leading to a diagnosis of Macrophage Activation Syndrome (MAS) and subsequent appropriate treatment. Upon the recurrence of symptoms following the completion of the prescribed medication, she was readmitted for further evaluation.

Case report

A young lady in her twenties, with a history of well-managed hypothyroidism and Systemic Lupus Erythematosus (SLE), presented with a three-month-long high-grade, continuous fever. This fever was accompanied by shivering, chills, and a rise in temperature during the evening. She also experienced abdominal pain and distension. About a month prior, she had a bleeding episode from the rectum (PR haemorrhage) that resolved spontaneously.

The patient underwent outpatient evaluation and was found to have pancytopenia, a condition characterized by low levels of all three types of blood cells. Bone marrow analysis showed elevated levels of histiocytes, hemophagocytes, and CD68 positivity. Suspecting SLE with Macrophage Activation Syndrome (MAS), she was treated with a three-day course of methylprednisolone pulse therapy. This led to a three-day period of being fever-free, but the fever and chills returned thereafter, prompting her admission for further assessment. Except for a positive family history of kala-azar (visceral leishmaniasis) in her father, the rest of her medical history was unremarkable.

Upon admission, she displayed dark brown macules on both arms, along with pitting edema, mild ascites, and moderate splenomegaly (enlarged spleen) upon abdominal examination. She had no other cardiovascular or neurological deficits. Her laboratory results showed elevated ferritin levels (>10,000), high triglyceride levels (337 mg/dL), reduced fibrinogen levels (98 mg/dL), and pancytopenia (Table 1). Tests for markers of a SLE disease flare were negative. Chest X-ray was normal with CECT abdomen showing pericardial and pleural effusion with hepatosplenomegaly.

Initial supportive treatment involved multiple transfusions of packed red blood cells and single-donor platelets to address her rectal bleeding. Due to persistent pancytopenia, her well-controlled SLE, and her residence in an area endemic for leishmaniasis, she underwent further evaluation for visceral leishmaniasis. A repeat bone marrow investigation revealed the presence of multiple LD bodies (Leishmania donovani amastigotes) along with hemophagocytes. This, combined with a positive serum rk39 test result and other laboratory findings, confirmed a diagnosis of visceral leishmaniasis with Hemophagocytic LymphoHistiocytosis (HLH).

Table 1: Laboratory investigations of the patient at admission and discharge.

Investigations	Admission	Discharge at 3 weeks
Hemoglobin (q/dL)	6.8	10.3
Total leucocyte count (x10 ul)	$0.72x10^3/\mu l$	$5.94x10^3/\mu l$
Platelet ($x10^3$ µl)	$9x10^3/\mu l$	$230x10^3/\mu l$
MCV (fl)	78.4 fl	80.9 f
Urea (mg/dL)	42 mg/di	19 mg/di
Creatinine (mg/dL)	0.4 mg/di	0.8 mg/di
ALT(U/L)	17 U/ L	46 U/L
AST(U/L)	54 U/ L	39 U/L
ALP (U/ L)	954 U/L	637 U/L
LDH(U/L)	796	4 13
Ferritin (ng/mL)	>10,000	1805
Triglyceride (mmol/ L)	337	310
CRP (mg/L)	33.8	6
C3 (mg/dL)	86	76
C4(mg/dL)	22	20

The patient was subsequently initiated on treatment with Intravenous Immunoglobulin (IVIg) and liposomal amphotericin B. She received a total of six doses, with a cumulative dose of 900 mg. After being fever-free for the past seven days, she was discharged in a stable hemodynamic condition.

Discussion

Here we find a rare case of a young female with SLE from a Leishmania endemic area presenting with HLH secondary to Visceral Leishmaniasis. Clinical manifestations of HLH (fever, hepatosplenomegaly, and pancytopenia) and visceral leishmaniasis (fever, hepatosplenomegaly, and pancytopenia) overlap, and laboratory testing is required to confirm that a patient has both conditions [5,6]. Infections, specifically EBV, are another primary cause of IAHS (infection-associated hemophagocytic syndrome, or HLH) [7]. Other viruses, bacteria, tuberculosis [8], malaria, and leishmaniasis have been reported to cause HLH due to infection. HLH is also associated with tumours, drugs, and autoimmune disorders, and it may develop during the course of X-linked lymphoproliferative syndrome, Chediak Higashi's, and Griscelli (type 2) syndromes [7]. Adults should be diagnosed with HLH using the HLH-2004 diagnostic criteria in conjunction with clinical judgement and patient history [9].

Leishmaniasis is characterised by multiple hematologic manifestations. These are caused by hemolysis, bone marrow replacement with leishmania-infected macrophages, haemorrhage, splenic sequestration of erythrocytes, hemodilution, and cytokine-mediated suppression of bone marrow. Even though autoimmunity is prevalent due to polyclonal B-cell activation, clinically evident hemolysis is uncommon in VL-associated HLH [7]. This is a first case where the patient had SLE as well as leishmania precipitating HLH making it a therapeutic challenge regarding maintaining balance between immunosuppression and antimicrobials. The clinical picture is rarely suggestive due to the overlapping clinical features, and bone marrow obtained for the diagnosis of suspected HLH may fail to reveal LD bodies. The first BMA frequently failed to establish the presence of LD bodies or HLH,

and was negative in 64.7% of cases for HLH and in 36.9% of cases for LD bodies at onset [10].

Given the problems of making a parasitological diagnosis at onset and the consequences of a delay in diagnosis, serology might be of value in therapy. Anti-rK39 ELISA has a sensitivity of 97% and a specificity of 98.9%, an earlier seroconversion, prognostic value, and a quicker turnaround time, making it a valuable serologic instrument [11]. Variable benefits have been reported for the use of IVIG in VL-associated HLH, which are likely related to the delay in initiating therapy. In the presence of hyperferritinemia, additional therapy with intravenous Immunoglobulin (IVIG), guided by clinical judgement, is required [12]. The majority of patients may not require adjunctive therapy, however, due to the expense of IVIG and the rapid resolution observed with antimicrobial treatment if the syndrome is recognised at its onset.

A systemic review by Rajagopala S et al. has reported a mortality of 14% in VL-HLH primarily because of infections or catastrophic bleeding. This may represent a substantial underreporting of VL-HLH mortality due to a lack of recognition or improved prognosis if identified early [10].

Our case of Visceral Leishmaniasis-associated Hemophagocytic Lymphohistiocytosis (VL-HLH) presents a significant therapeutic challenge and diagnostic puzzle. This is due to the patient also having Systemic Lupus Erythematosus (SLE), where the symptoms of SLE disease flare closely resemble the clinical findings of both VL and HLH. To the best of our knowledge, this is the first documented instance of successful treatment for VL-HLH in a patient concurrently diagnosed with SLE.

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