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CASE REPORT

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Scrub typhus complicating hemophagocytic lymphohistiocytosis: a case report.

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder characterised by uncontrolled activation of CD8+ T lymphocytes and macrophages, resulting in organ damage. While primary HLH is associated with genetic defects, secondary HLH can be triggered by infections, malignancies, or autoimmune disorders. Scrub typhus-induced HLH underscores the importance of considering tropical fevers as potential triggers for HLH. We present the case of a 27-year-old man who was admitted with no known comorbidities, who had multiple complaints of loose stool for the past 10 days,, fever for the past 8 days and dry cough for the past 3 days. The initial investigation showed bicytopenia, transaminitis, and hyponatremia. A tropical fever study was done, which was negative for typhoid fever, dengue, malaria, HIV, and viral hepatitis. Scrub IgM turned out to be positive. EBV IgM was negative, and Leptospira IgM was negative. The patient was treated with IV antibiotic doxycycline. Since the patient's counts did not improve and had a daily fever spike despite being on antibiotic. On the basis of the H score, the probability of HLH came out. Due to high suspicion of HLH, pulse steroids (1 g of methylprednisolone for 3 days) were started and monitored for counts and fever spikes, which settled after the course of steroids. At follow-up, the patient had no episodes of fever, and the bicytopenia resolved. Early recognition and intervention are crucial for reducing mortality in HLH. This case report contributes to pathophysiology, diagnosis and management the understanding of HLH, highlighting the need for vigilance in patients presenting with scrub typhus and associated complications.

KEY WORDS: Hemophagocytic lymphohistiocytosis, scrub typhus, tropical fever.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder associated with unremitting activation of CD8+ T lymphocytes and macrophages that leads to organ damage. HLH is usually associated with genetic defects in cytotoxicity of T cells and natural killer (NK) cell cytotoxicity. HLH can be classified as primary and secondary HLH. Primary HLH is caused by a genetic mutation that affects the immune system. It is characterised by macrophages that release too many pro-inflammatory cytokines, which leads to hyperinflammation [1]. Secondary HLH is secondary to infections, malignancies, and autoimmune disorders. The most common infection associated with HLH is the Epstein Barr virus [2-4]. Scrub typhus is a rare but important secondary cause of hemophagocytic lymphohistiocytosis (HLH), and its rare presentation can complicate diagnosis and treatment. This can result in delays that can lead to serious complications, such as secondary infections, sepsis, and multiorgan dysfunction [5-7].

This case report aims to illustrate the uncommon complication of hemophagocytic lymphohistiocytosis (HLH) arising from scrub typhus and to underscore the importance of a thorough diagnostic evaluation in the management of these patients.

CASE REPORT

PATIENT INFORMATION: A 27-year-old male who was admitted with no known comorbidities, presented with complaints of multiple episodes of loose stool for the past 10 days not associated with blood and mucous in the stool, fever for the past 8 days documented up to 102 degrees Fahrenheit, which was associated with chills and rigour, continuous type, not relieved with medication, and dry cough for past 3 days.

CLINICAL FINDINGS: On physical examination, the patient was conscious and orientated, blood pressure 100/70 mmHg, heart rate 83/minutes, saturation 98%, no pallor, no cyanosis, no pedal edema. The patient had icterus, cervical lymphadenopathy of level 1b, and 2 bilaterally of an approximate size of 0.5-1 cm. The abdomen examination did not show hepatosplenomegaly, bilateral normal vesicular breath sounds in the chest, central nervous system - no meningeal signs, cardiovascular system - S1S2 heard without audible murmur.

TIMELINE: The patient was admitted with complaints of multiple episodes of loose stool in the past 10 days, fever for the past 8 days, and dry cough in the past 3 days. On day 1 of admission, the patient was started on IV doxycycline. However, on day 5, there was no improvement in total leukocyte count, and the patient continued to experience daily fever spikes despite antibiotic treatment. Additional investigations were conducted to rule out other causes of cytopenia. Given the high suspicion of HLH, pulse steroid therapy was started on day 5. On day 7 onward, the leukocyte count improved and the fever subsided. The patient was discharged on day 10 with a tapering dose of steroids. On day 15, the patient had no further fever episodes and bi-cytopenia had resolved.

DIAGNOSTIC ASSESSMENT: The initial investigation showed bicytopenia (a condition where there is a reduction in two of the three blood cell lines: erythrocytes, leukocytes, or platelets), transaminitis, and hyponatremia. Peripheral smear showed leucopenia with thrombocytopenia and some giant platelets. CRP (6.7mg/dL) was also raised. A tropical fever study was done, which was negative for typhoid fever, dengue, malaria, HIV, and viral hepatitis. Scrub IgM turned out to be positive. EBV IgM was negative, and Leptospira IgM was negative. The entire USG abdomen was normal, with no lymph nodes and hepatosplenomegaly. Since the patient's counts did not improve and had a daily fever spike despite taking antibiotics, further investigations were done to rule out other causes of cytopenia. Ferritin was raised (>1000 ng/ml), triglycerides increased (268 mg/dl), fibrinogen was mildly decreased slightly (205 U/L), and LDH increased (4043 U/L) (Table 1).

Table 1. Investigations during hospital stay.

Investigations	Day 1	Day 3	Day 5	Day 7	Day 8	Day 9
Hemoglobin (g/dL) (normal range 14-17.4g/dl)	11.2	11.0	11.5	9.8	9.3	10.2
Total Leukocyte Count (µL) (normal range 4000-11000µL)	4500	2000	2500	3300	4000	6000
Platelets (µL) (normal range 1.5-4.5 lakh/µL)	30,000	20,000	<20,000	45000	70,000	1.3L
Urea/Creatinine (mg/dL) (normal range 15-45mg/dl)	24/0.7	33/0.98	20/0.8	19/0.6	14/0.5	22/0.5
Total bilirubin (mg/dL) (Total bilirubin normal range 1.2 - 1.2 mg/dl) (Direct bilirubin normal range .1-.3mg/dl)	2.63/1.4	1.71/1.02	2/1.04	0.89/0.21	1.01/0.33	0.9/0.2
Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) (U/L) (AST normal range 15-50 U/L) (ALT normal range 15-50 U/L)	488/192	1382/349	1047/341	491/218	326/179	187/172
Sodium/Potassium (mmol/L) (Sodium normal range 130-150 mmol/L)	128/3.6	126/4.02	121/3.5	132/4.77	141/4.1	143/4.9

THERAPEUTIC INTERVENTION: The patient was treated with IV antibiotic doxycycline. Since patient counts did not improve and had a daily fever increase despite being on antibiotic.Based on the H score [8], the probability of HLH was elevated. Due to high suspicion of HLH, pulse steroids (1 g of methylprednisolone for 3 days) were started and monitored for counts and fever spikes, which settled after the course of steroids (Table 2).

Table 2. Scoring systems for the diagnosis of secondary HLH - H Score.

Parameter	Criteria for scoring	Scoring
Known underlying immunosuppression (HIV positive/on glucocorticoids, immunosuppressant's)	No	0
	Yes	+18
High temperature (Degrees Fahrenheit)	<101.1	0
	101.1-102.9	+33
	>102.9	+49
Organomegaly	No	0
	Hepatomegaly (or) Splenomegaly	+23
	Hepatomegaly (and) Splenomegaly	+38
Hyperferritinemia (ng/ml)	<2000	0
	2000-6000	+35
	>6000	+50
Cytopenia	1 lineage	0
	2 lineages	+24
	3 lineages	+34
Hemophagocytosis features in bone marrow aspirate	No	0
	Yes	+35
Hypertriglyceridemia (mg/dl)	<132	0
	132-354	+44
	>354	+64
Hypofibrinogenemia (mg/dl)	>250	0
	<=250	+30
Elevated Alanine aminotransferase (ALT) (U/L)	<30	0
	>30	+19

FOLLOW-UP AND OUTCOMES: The patient was discharged on the 10th day of admission with tapering steroids (prednisolone 40 g with weekly tapering). After the 15th day of discharge, at follow-up, the patient had no episodes of fever and bi-cytopenia resolved.

DISCUSSION

Hemophagocytic lymphohistiocytosis has a varied presentation but is most commonly associated with fever, splenomegaly, and cytopenia [9]. Our patient did not present with splenomegaly.A retrospective study at the Mayo Clinic identified 62 adults with HLH. The majority had a malignancy (52%), followed by infection (34%), autoimmune disorders (8%), and an idiopathic cause of HLH (6%) [10].

Scrub typhus as a cause of HLH has been described only as case reports in the literature. A study by Jin Y et al. showed complications such as ARDS and DIC secondary to scrub typhus-induced HLH [11]. This case showed characteristics according to the proposed diagnostic criteria but had a high probability score of HLH based on the H score [8].

Although hemophagocytosis is the pathological hallmark of HLH, it is important to note that it is neither sensitive nor specific. The sensitivity to finding hemophagocytosis in the marrow is increased by staining for CD163, which specifically highlights macrophages. NK cell activity is part of the diagnostic criteria for paediatric HLH, but this test is rarely helpful in the adult population [12]. This case report also focusses on the importance of incorporating other parameters with modifying HLH as bone marrow hemophagocytosis is neither sensitive nor specific for HLH, nor it is feasible in all clinical settings.

Secondary HLH, when induced by infections, is first treated with infection-specific antibiotics and supportive measures. This case did not respond to antibiotics and corticosteroid administration showed improvement in symptoms and cytopenias. This warrants further changes in the management of HLH. HLH is a life-threatening disease and is often missed in adults. It should be suspected in patients with tropical fevers, especially in the presence of multi-organ failure, persistent high fever, and variable cytopenia. Early diagnosis and effective early therapy could reduce mortality [2].

PATIENT PERSPECTIVE: After discharge, at follow-up, the patient had no episodes of fever and bi-cytopenia resolved. HLH is a potential complication for any tropical infection and should be suspected in patients with relentless fever. Early initiation of treatment improves the patient's outcome and prevents further complications.

CONCLUSIONS

This case involves scrub typhus complicated by hemophagocytic lymphohistiocytosis, initially treated with IV doxycycline. However, the patient did not show any improvement, with persistent fever and no change in leukocyte count. HLH was confirmed using the H score, which included elevated temperature, cytopenia, hypofibrinogenemia, hypertriglyceridemia, and elevated alanine aminotransferase levels. After the patient did not respond to antibiotics, pulse steroid therapy was initiated, which led to an improvement in leukocyte count and a resolution of the fever.

SUPPLEMENTARY INFORMATION

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Informed Consent Statement: *Informed consent was obtained from all subjects involved in the study.*
Data Availability Statement: *The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.*
Conflicts of Interest: *The authors declare no conflicts of interest.*

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