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Rare case of post-infectious HLH presenting as Panniculitis

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Abstract
Hemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening hyperinflammatory syndrome characterized by uncontrolled activation of immune cells. It can be categorized into primary and secondary HLH, with the latter often triggered by infections, malignancies, or autoimmune diseases. This abstract provides an overview of HLH, including its clinical features, diagnostic criteria, and treatment approaches. HLH typically presents with fever, hepatosplenomegaly, cytopenias, and hyperferritinemia. Diagnostic criteria include genetic mutations, elevated inflammatory markers, and evidence of hemophagocytosis. Treatment involves immunosuppression, with a combination of chemotherapy, corticosteroids, and hematopoietic stem cell transplantation being the mainstay. Despite advancements in its understanding and management, HLH remains a diagnostic challenge due to its varied presentation and overlapping features with other conditions. Early recognition and timely intervention are crucial in improving outcomes for patients with HLH. Further research is needed to enhance our understanding of the underlying mechanisms and to develop targeted therapies for this complex disorder.

Keywords: Biopsy, Lymphohistiocytosis, Hemophagocytic, Lymphoma, Subcutaneous panniculitis-like T cell lymphoma**,** Hemophagocytic lymphohistiocytosis

Introduction
Hemophagocytic lymphohistiocytosis (HLH) is a serious and life-threatening condition characterized by an abnormal and excessive immune response. It involves the proliferation and activation of macrophages, which leads to the suppression of bone marrow function and the occurrence of intense phagocytosis in the bone marrow and liver [1]. Although HLH is most commonly observed in infants from birth to 18 months old, it can also affect individuals of all ages, including children and adults [2]. This condition can be triggered by various factors that disrupt the normal balance of the immune system. Infections, both in individuals with a genetic predisposition and in sporadic cases, are a common trigger for HLH [3, 4]. Panniculitis-like T cell lymphoma can lead to HLH in 15-25% of cases. HLH is a severe inflammation triggered by cytokine overproduction from activated T cells and histiocytes. It can be caused by viruses, rheumatic diseases, and tumors. Histopathological findings show widespread lymphocyte and macrophage accumulation in multiple organs [5].
In this case report, we present a rare occurrence of post-infectious hemophagocytic lymphohistiocytosis (HLH) manifesting as panniculitis, highlighting the unusual clinical presentation and the challenges faced in its diagnosis and management.

Case Report
A 40-year female housewife from Malegaon visits our emergency department with a complaint of reduced urine output for 7 days, a rash over the abdomen for 5 days, and fever that was high grade and intermittent in type. The rash was initially maculopapular, which eventually formed blebs and sloughed off superficial skin and then progressed to overt ulcer with panniculitis, in addition to this she was also icteric and complained of progressive breathlessness. The only relevant recent medical history was that she had suffered from acute gastroenteritis three weeks ago, which had subsided with the help of medication provided by a local practitioner, and she has no significant personal, obstetric, or family history that could be related to her current clinical presentation.

After that, she developed the above complaints for which she was referred to our hospital for further management. The patient was conscious, well-oriented, and responsive to commands. On examination, her pulse was regular at 112 beats per minute, her blood pressure was 100/60 mmHg, and her oxygen saturation was 99% on 6 L of oxygen. Her respiratory rate was 24 breaths per minute. She demonstrated pallor, icterus, and pedal edema, with a positive jugular venous pulse. No signs of cyanosis, clubbing, or lymphadenopathy were observed. On inspection, no significant abnormalities were noted. During palpation, a palpable spleen was detected on abdominal examination, but no other organomegaly was appreciated. Auscultation of the respiratory system revealed fine basal crepitations.

Table 1: Investigational test of current case report and its outcomes

Investigations	Result
Hemoglobin	6.8
Leukocytes	24,200 (90% Neutrophils)
Platelets	48,000
Blood smear	Microcytic hypochromic
Ferritin	469
D dimer	6.9
Sr. LDH	264
Retic count	2.1%
DCT/IDCT	Negative
Fibrinogen	106 mg/dl
ESR	120
CRP Quantitative	83.7
Procalcitonin	25.3 ng/ml
Liver function tests	AST: 21.0 Sr. Bilirubin Total: 7.6, Sr. Bilirubin Direct: 4.9, Sr. Bilirubin Indirect: 2.7
Renal function test	Blood urea: 167, Serum creatinine: 4.9, Sr. Calcium: 7.0, Sr. Uric Acid: 11.0
Serum electrolytes	Sr. Sodium/Potassium/Chlorides 126/4.5/103 ABG (Metabolic acidosis): 7.23
ANA	Negative
PT/INR	31/2.2
PTT Ratio	2.8 (98.0/35.0 seconds)
HCV/HBV/HIV Tri Dot	Non-Reactive
Hep A/E	Negative IgM
Dengue-NS1 (Rapid)	Non-Reactive
Dengue-IgM (Rapid)	Non-Reactive
Leptospirosis-IgM	Negative

The case was initially presumed to be Septic shock with MODS, DIC and AKI secondary to abdominal wall cellulitis and panniculitis, the cause of which was unknown, based on the findings from the investigations in (Table 1). The patient underwent alternate-day dialysis during the first week, resulting in improved urine output, renal function test results, and symptom relief. Surgical debridement of the ulcer was performed twice, removing all necrotic tissue, and revealing healthy granulation tissue. Subsequently, the patient's renal and liver function tests improved, and her hemodynamic status stabilized without the need for inotropic support. However, persistent anemia and thrombocytopenia, despite multiple transfusions, raised suspicion of hemophagocytosis. Consequently, a bone marrow biopsy was conducted, confirming the presence of hemophagocytosis. The patient met the diagnostic criteria for HLH and was treated with Dexamethasone (initially 10 mg/m2 for two weeks followed by 5 mg/m2 for two weeks followed by slowly tapering the dose) resulting in significant improvement. Following several flap surgeries, the patient was eventually discharged from the hospital. (Figure 2).

Fig 1: Panniculitis of the lower abdomen (2 days post presentation to hospital)

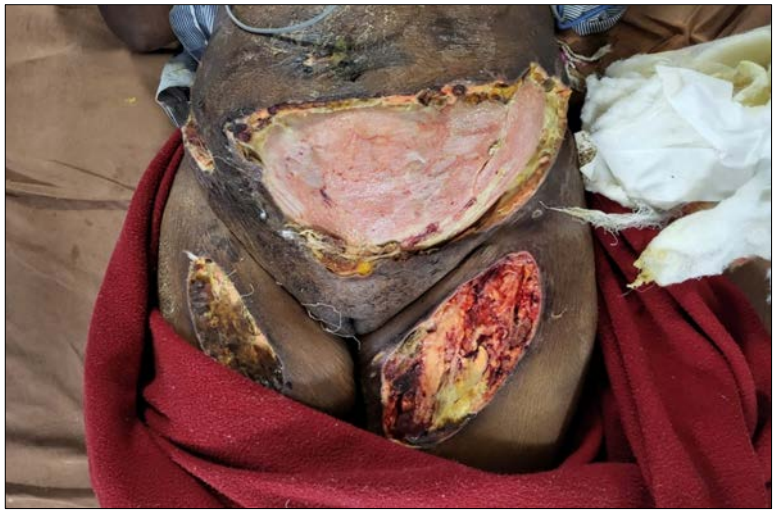

Fig 2: Post-surgical debridement of slough and entire fat pad

Maratha VidyaPrasarakSamaj, Nahsik

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DEPARTMENT OF PATHOLOGY

BONE MARROW ASPIRATION CYTOLOGY REPORT

ytopath No. BM 23/22 Date 02/5/22

ame: Mrs. Arunabai Mali

ge: 32 years Sex: Female

eferred by Dr. Dept. : MICU

pecimen Sent : Bone marrow aspiration

linical History: C/o persistent anemia

linical Diagnosis:

eceived on:

PERIPHERAL BLOOD SMEAR

Red Blood Cells- Mild anisopoikilocytosis with predominantly normocytic normochromic. (Multiple transfusion given)

White Blood Cells – Within normal limits

Neutrophils - 71%; Lymphocytes -25 %; Monocytes - 03%; Eosinophils -01 %;

Basophils – 00%

Platelets – Adequate on smears. Macroplatelets are seen.

No evidence of hemoparasite seen.

Retic count –<0.5%

BONE MARROW ASPIRATION CYTOLOGY :

Fragments : Seen

Cellularity: Adequate.

M:E Ratio : 4:1

Erythroid Series –Suppressed and show normoblastic maturation. Dyserythropoiesis noted.

Myeloid series – Normal maturation and morphology. Blasts cells are less than 20%.

Megakaryocytes – Seen.

No evidence of atypical cells or granuloma.

Occasional plasma cells and lymphocytes are seen within normal limits.

There is evidence of haemophagocytosis.

No abnormal cells detected.

Impression – Suppression of Erythroid Series.

Bone marrow biopsy report is awaited.

Dr. Sheela Chikhalikar (MD Pathology) Assistant Professor

Dr. Shubhangi Rairikar (MD Pathology) Associate Professor

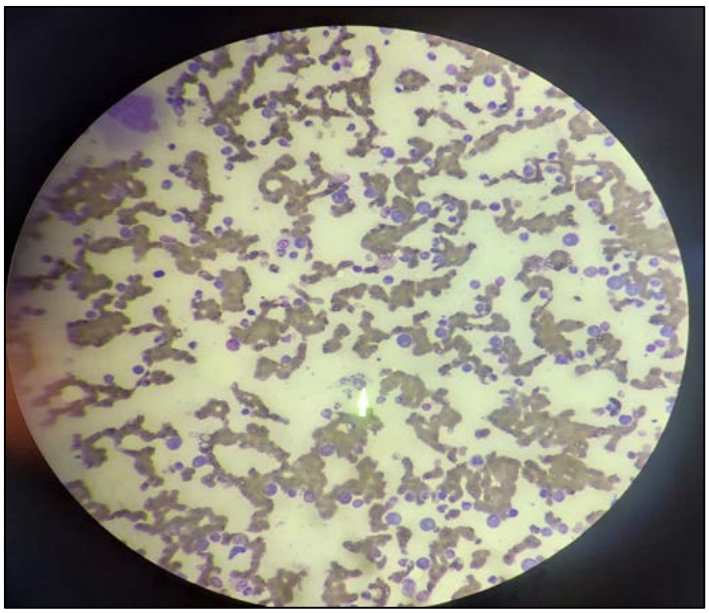

Fig 3: Bone Marrow Biopsy: Evidence of hemophagocytosis and Suppression of Erythroid series

Discussion

Criteria for diagnosis of HLH syndrome

Five out of the following eight conventional criteria

- Hemophagocytosis the BM/ spleen/ lymph nodes.
- Serum ferritin more than or equal to 500 ug/L.
- Hypofibrinogenemia (fibrinogen less than or equal to 1.5 g/L) or hypertriglyceridemia (triglycerides more than or equal to 3 mmol/L).
- Low NK cell activity.
- Elevated soluble IL-2 receptor (CD25) more than or equal to 2400 U/mL.
- Bi- or Tri cytopenia.
- Splenomegaly.
- Fever.

HLH is a condition of uncontrolled immune system stimulation that can occur as a primary or acquired disorder. Clinical manifestations of HLH include fever, organ enlargement, and weight loss. In addition, laboratory tests typically show bi-cytopenia or pancytopenia, cytolysis and cholestasis, serum ferritin elevation, and clotting disorders [6]. Hematologic malignancies are the main disorder associated with hem phagocytic syndrome in young people and these patients have a high risk of early mortality. The management and diagnosis of hem phagocytic lymphohistiocytosis in young remain unresolved, with a clinical spectrum that ranges from mild to rapidly fatal multi-organ failure. Inherited HLH can be in early childhood without specific treatment [7].

The primary aim of therapy is to suppress the life-threatening inflammation associated with HLH by targeting immune cells. Induction therapy, based on the HLH-94 protocol, involves weekly treatments with dexamethasone and etoposide. Intrathecal methotrexate and hydrocortisone are administered to those with central nervous system involvement. Patients who show signs of recovery during induction therapy are gradually tapered off treatment, while those who do not exhibit improvement continue therapy as a bridge to allogeneic hematopoietic cell transplantation (HCT). HCT is indicated for patients with an HLH gene mutation, central nervous system disease, or disease relapse.

The authors highlight the importance of considering HLH as a differential diagnosis in patients presenting with panniculitis, especially in the presence of other clinical and laboratory findings suggestive of HLH. Prompt diagnosis and treatment are crucial in achieving good clinical outcomes in patients with HLH.

A similar study was performed by Mody A, *et al.* [5] present a case report of a 48-year-old male patient who presented with tender, erythematous nodules on his right thigh and left arm. Despite several rounds of antibiotics, there was no substantial improvement in the patient's condition. A skin biopsy revealed CD3/CD8 lymphocytic rimming of the adipocytes, leading to the diagnosis of subcutaneous panniculitis-like T-cell lymphoma. The case emphasizes the significance of promptly performing a biopsy on skin lesions that do not respond to conventional treatment. This approach is crucial for obtaining an accurate diagnosis and initiating timely treatment, thereby preventing adverse outcomes.

Conclusion

Hemophagocytic Lymphohistiocytosis is a very rare condition with varied presentations which requires high suspicion for diagnosis. According to a nationwide cohort study in England, reported crude incidence rate of HLH is around 4 per million persons per year. This case showed an even rarer presentation of Panniculitis. Due to the awareness about this condition and timely treatment, the patient's condition improved miraculously.

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