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HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS PRESENTING AS PERSISTENT FEVER AND PANCYTOPENIA: A RARE CASE REPORT

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ABSTRACT

Background: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disorder of excessive activation of macrophages and lymphocytes that can result in overwhelming inflammatory responses, multi-organ failure, and death. The nonspecific symptoms and signs of HLH can lead to significant diagnostic delays

Case Presentation: A 42-year-old male was admitted with high-grade fevers, fatigue, anorexia, weight loss and progressing pancytopenia. Physical examination was notable for pallor and hepatosplenomegaly. Work-up was positive for severely reduced blood counts, markedly elevated ferritins (18,500 ng/mL), triglycerides, and decreased fibrinogen; liver enzymes and lactate dehydrogenase were elevated. Work-up for infection, autoimmunity, and malignancy was negative. Bone marrow biopsy demonstrated considerable hemophagocytosis. This patient met the diagnostic criteria for HLH-2004 and had a diagnosis of secondary HLH. The patient responded to dexamethasone and etoposide treatment in combination with general supportive care.

Conclusion: HLH should be considered in patients presenting with prolonged fever, cytopenias, and unexplained systemic inflammation. Early recognition, prompt diagnostic evaluation, and timely initiation of therapy are essential for improving survival and preventing disease-related complications.

KEYWORDS: Hemophagocytic lymphohistiocytosis, HLH, Pancytopenia, Persistent fever, Hyperferritinemia, Hemophagocytosis, Cytokine storm, Etoposide

1. INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening hyperinflammatory condition characterized by the excessive activation and proliferation of macrophages, natural killer (NK) cells and cytotoxic T lymphocytes. Overstimulation of the immune system leads to the exaggerated secretion of inflammatory cytokines (cytokine storm), resulting in damage to organs throughout the body. HLH may occur in people of all ages and may be subdivided into primary (familial) or secondary (acquired) forms, which differ in their causes and mechanisms. Genetic causes for immune system dysregulation underlie the primary form of the disease, whereas the secondary form may be triggered by underlying infections, tumors, autoimmune disease or immunosuppression. Diagnosis of HLH is often challenging due to signs and symptoms that are similar to those seen in other conditions such as severe infections, sepsis and hematological cancer.[1,2]
The pathophysiology of HLH is thought to include diminished function of cytotoxic NK cells and CD8+ T lymphocytes, which may lead to continuous activation of macrophages and overproduction of pro-inflammatory cytokines including: interferon-gamma, tumor necrosis factor-alpha, interleukin-1, interleukin-6, and interleukin-18. These cytokines can lead to fever, cytopenias, hepatic dysfunction, coagulopathy, and infiltration of organs with activated immune cells. Hemophagocytosis, or the engulfment of red blood cells, other leukocytes, their precursors and platelets by activated macrophages in bone marrow and other reticuloendothelial tissues, is a key histopathologic finding in HLH and can contribute substantially to pancytopenia and other cytopenias. If unaddressed, disease can rapidly advance to multi-organ failure and death.[3,4]
Secondar HLH is being diagnosed more frequently in the adult patients and the frequent cause is infection which can be viral like EBV, CMV, HIV, or severe bacterial, fungal or parasitic infections. Other frequent cause in the adult patients

are hematologic malignancies especially lymphomas.Autoimmune disease and rheumatologic disorders can also cause HLH such as SLE and adult-onset still disease. It is believed that the incidence of adult HLH is being underestimated because it is being missed or delayed due to lack of diagnosis. Clinical presentation can be diverse and often includes high fever, splenomegaly, lymphadenopathy, cytopenia, high ALT/AST levels, hypertriglyceridemia,hypofibrinogenemia and severely increased ferritin level.[5,6]
Diagnosis is typically made using the HLH-2004 diagnostic criteria. According to these, patients have to fulfil at least five of the following eight clinical and laboratory findings: fever, splenomegaly, cytopenia of at least two blood cell types, hypertriglyceridemia and/or hypofibrinogenemia, detection of hemophagocytosis, low or absent NK-cell function, high soluble IL-2 receptor levels and hyperferritinemia. High serum ferritin level is one of the key criteria. In the context of investigations of HLH, bone marrow examination may still be helpful in documenting hemophagocytosis and excluding other conditions like leukemia, lymphoma or aplastic anemia. Early detection of HLH is important as there is significantly increased morbidity and mortality due to the delay of diagnosis.[7,8]
We report a unique case of secondary HLH in a middle-aged adult with sustained fever, progressive pancytopenia, and systemic signs of malaise and constitutional illness, including hepatosplenomegaly. Initially, multiple clinical investigations and tests were negative and unsuccessful to determine the exact etiology, such as any infectious, autoimmune, or malignancy process. Definitive diagnosis was made by demonstration of marked hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, and bone marrow confirmation of hemophagocytosis. Administration of therapy based on dexamethasone and etoposide yielded excellent and sustained clinical remission and complete hematological recovery. HLH must be an included condition in the diagnosis of febrile syndrome with pancytopenia of unknown origin; therefore early diagnosis and treatment can lead to better outcomes for the patient.[9,10]

CASE PRESENTATION

Patient Demographics

A 42-year-old male presented to the Department of General Medicine of a tertiary care teaching hospital with complaints of persistent high-grade fever, progressive generalized weakness, and loss of appetite for six weeks. The patient was a married farmer from a rural area and belonged to a middle socioeconomic background. He was conscious, oriented, and cooperative during the examination.

Chief Complaints

The patient presented with the following complaints:

- Persistent high-grade fever for 6 weeks
- Generalized weakness and fatigue for 5 weeks
- Loss of appetite for 4 weeks
- Unintentional weight loss (approximately 8 kg) over 2 months
- Occasional night sweats for 3 weeks

History of Present Illness

The patient was well until six weeks before admission, when he developed episodes of high-grade fever of 39-40C with chills and rigors intermittently. Antipyretics partially relieved the fever initially but it occurred daily. This was followed by the onset of gradually increasing weakness and fatigue, and significantly reduced exercise tolerance in the ensuing weeks, impacting daily activities. He also complains of diminished appetite and significant weight loss of about 8 kg over the last two months. The patient denies having any cough, expectoration, hemoptysis, abdominal pain, diarrhea, vomiting, urinary symptoms, skin rashes, joint pains, headache, altered sensorium, seizures or bleeding tendency. He has received several courses of empirical antibiotic treatment from the local physicians without any improvement in his symptoms. Because of persistent symptoms and worsening of fatigue he was referred to our tertiary center.

Past Medical History

The patient had no known history of any disease and there was no history of previous hospitalizations or major surgical procedures.

Medication History

Before admission, the patient had received:

- Oral Paracetamol 650 mg as needed for fever
- Oral Amoxicillin-Clavulanic Acid 625 mg twice daily for 7 days
- Oral Azithromycin 500 mg once daily for 5 days
- Multivitamin supplements

Despite these treatments, fever persisted and symptoms progressively worsened. No history of immunosuppressive medications, corticosteroid therapy, chemotherapy, or herbal medicine use was reported.

Family History

There was no known family history of any disease.

Social History

The patient was married and lived with his family.

Non-smoker

- Occasional alcohol consumption
- No history of recreational drug use
- No recent travel history
- No history of high-risk sexual behavior
- No known exposure to tuberculosis patients

The patient reported adequate dietary intake prior to illness but experienced significant appetite loss during the course of his disease.

Occupational History

The patient worked as a farmer and was regularly involved in agricultural activities.
He reported:

- Frequent exposure to soil and standing water
- Outdoor work for prolonged periods
- No exposure to industrial chemicals or radiation
- Allergic History

The patient had:

- No known drug allergies
- No food allergies
- No history of allergic rhinitis
- No history of asthma
- General Physical Examination

Upon admission:

Parameter	Findings
Temperature	39.2°C
Pulse Rate	108 beats/minute
Blood Pressure	110/70 mmHg
Respiratory Rate	20 breaths/minute
Oxygen Saturation	98% on room air
Height	170 cm
Weight	62 kg
BMI	21.5 kg/m²

General Examination Findings

- Pallor: Present
- Icterus: Absent
- Cyanosis: Absent
- Clubbing: Absent
- Lymphadenopathy: Absent
- Pedal edema: Absent
- Dehydration: Mild

Systemic Examination
Cardiovascular System

- S1 and S2 heard normally
- No murmurs
- No added sounds

Respiratory System

- Bilateral air entry equal
- No wheeze or crepitations

Central Nervous System

- Conscious and oriented
- No focal neurological deficits
- Cranial nerves intact

Gastrointestinal System

- Mild hepatomegaly (liver palpable 3 cm below right costal margin)
- Splenomegaly (spleen palpable 4 cm below left costal margin)
- No ascites
- Bowel sounds normal
- Laboratory Investigations

Complete Blood Count

Parameter	Value	Reference Range
Hemoglobin	7.8 g/dL	13–17 g/dL
RBC Count	2.9 $\times 10^{12}$/L	4.5–5.9 $\times 10^{12}$/L
Total WBC Count	2.1 $\times 10^{9}$/L	4–11 $\times 10^{9}$/L
Neutrophils	42%	40–70%
Lymphocytes	48%	20–45%
Platelet Count	68 $\times 10^{9}$/L	150–450 $\times 10^{9}$/L
ESR	72 mm/hr	<20 mm/hr

Peripheral Blood Smear

- Normocytic normochromic anemia
- Leukopenia
- Thrombocytopenia
- No blast cells
- No hemoparasites identified

Liver Function Tests

Parameter	Value	Reference Range
AST	145 U/L	<40 U/L
ALT	128 U/L	<41 U/L
ALP	185 U/L	44–147 U/L
Total Bilirubin	1.2 mg/dL	0.3–1.2 mg/dL
Serum Albumin	3.0 g/dL	3.5–5.0 g/dL

Renal Function Tests

Parameter	Value	Reference Range
Blood Urea	28 mg/dL	15–40 mg/dL
Serum Creatinine	0.9 mg/dL	0.6–1.2 mg/dL

Inflammatory Markers

Parameter	Value	Reference Range
CRP	85 mg/L	<10 mg/L
ESR	72 mm/hr	<20 mm/hr
LDH	1200 U/L	140–280 U/L

Ferritin and Lipid Profile

Parameter	Value	Reference Range
Serum Ferritin	18,500 ng/mL	30–400 ng/mL
Triglycerides	425 mg/dL	<150 mg/dL
Total Cholesterol	142 mg/dL	<200 mg/dL

Coagulation Profile

Parameter	Value	Reference Range
PT	16.5 seconds	11–14 seconds
INR	1.4	0.8–1.2
Fibrinogen	120 mg/dL	200–400 mg/dL

Other Blood and Culture tests

Investigation	Result
Blood Culture	Negative
Urine Culture	Negative
HIV ELISA	Negative

HBsAg	Negative
Anti-HCV	Negative
Dengue NS1 Antigen	Negative
Malaria Parasite Test	Negative
Widal Test	Negative
Tuberculosis GeneXpert	Negative

Autoimmune Tests

Investigation	Result
ANA	Negative
Rheumatoid Factor	Negative
Anti-dsDNA	Negative
Complement Levels	Normal

Radiological Investigations

Chest X-Ray

- No active pulmonary pathology
- No pleural effusion

Ultrasonography Abdomen

- Mild hepatomegaly (16.8 cm)
- Moderate splenomegaly (15.2 cm)
- No focal lesions
- No ascites

Contrast-Enhanced CT Abdomen

- Hepatosplenomegaly
- No lymphadenopathy
- No intra-abdominal mass lesion

Bone Marrow Examination

Bone Marrow Aspiration

- Microscopic examination revealed:
- Hypercellular marrow
- Numerous activated macrophages
- Evidence of hemophagocytosis
- Phagocytosed erythrocytes, leukocytes, and platelets
- No evidence of leukemia or lymphoma infiltration

Bone Marrow Biopsy

- Hypercellular marrow
- Increased histiocytic activity
- Marked hemophagocytic activity

Bone Marrow Diagnosis

- Features consistent with Hemophagocytic Lymphohistiocytosis (HLH).

DIAGNOSIS

Based on the patient's clinical presentation of persistent high-grade fever, progressive generalized weakness, significant weight loss, hepatosplenomegaly, and pancytopenia, along with characteristic laboratory findings including severe hyperferritinemia (18,500 ng/mL), hypertriglyceridemia, hypofibrinogenemia, elevated lactate dehydrogenase, and abnormal liver function tests, a diagnosis of Secondary Hemophagocytic Lymphohistiocytosis (HLH) was established. Bone marrow aspiration and biopsy demonstrated prominent hemophagocytosis, confirming the hyperinflammatory state. The patient fulfilled eight HLH-2004 diagnostic criteria, including fever, splenomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis, hyperferritinemia, and elevated soluble interleukin-2 receptor levels, thereby confirming the diagnosis of secondary HLH.

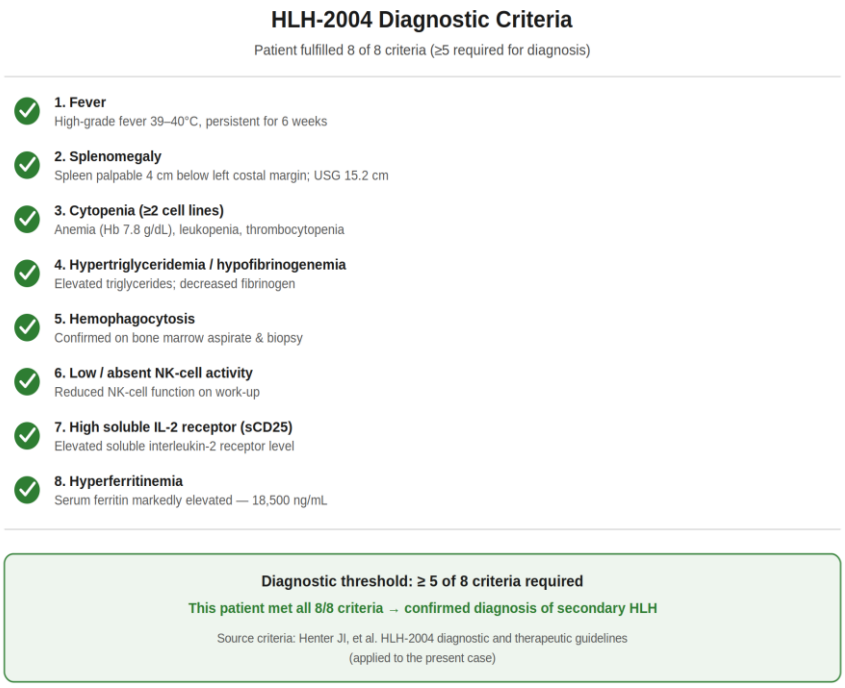

Figure 1: Application of the HLH-2004 diagnostic criteria to the reported case. The patient fulfilled all eight criteria, exceeding the threshold of five required for diagnosis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for this patient included severe sepsis, disseminated tuberculosis, hematological malignancies such as acute leukemia and lymphoma, aplastic anemia, megaloblastic anemia, autoimmune diseases including systemic lupus erythematosus, and macrophage activation syndrome. These conditions were considered because they can present with prolonged fever, constitutional symptoms, hepatosplenomegaly, and pancytopenia. Extensive microbiological investigations, including blood cultures and tuberculosis testing, were negative. Autoimmune screening showed no evidence of connective tissue disorders, while bone marrow examination excluded leukemia, lymphoma, and aplastic anemia. The presence of marked hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, elevated inflammatory markers, and hemophagocytosis strongly favored a diagnosis of secondary hemophagocytic lymphohistiocytosis (HLH).

TREATMENT

Week 1 : Following diagnosis of HLH, the patient was admitted and initiated on Dexamethasone 10 mg/m²/day IV once daily and Etoposide 150 mg/m² IV on Days 1 and 4. Supportive management included Normal Saline 1000 mL IV twice daily, Pantoprazole 40 mg IV once daily, and Paracetamol 650 mg orally as needed for fever. Due to severe anemia (Hb 7.8 g/dL), two units of packed red blood cells were transfused. Empirical Piperacillin-Tazobactam 4.5 g IV every 8 hours was initiated while awaiting infectious lab test results.

Week 2 : The patient continued Dexamethasone 10 mg/m²/day IV and received Etoposide 150 mg/m² IV on Days 8 and 11. Fever frequency gradually decreased and appetite showed improvement. Since blood cultures and infectious investigations remained negative, empirical antibiotics were discontinued. Trimethoprim-Sulfamethoxazole 160/800 mg orally three times weekly and Fluconazole 200 mg orally once daily were started for opportunistic infection prophylaxis. Pantoprazole was continued, and serial monitoring of blood counts, ferritin, triglycerides, and liver function tests was performed.

Week 3 : With early clinical response, dexamethasone was tapered to 5 mg/m²/day orally once daily, while Etoposide 150 mg/m² IV was administered on Day 18. The patient remained clinically stable with fewer febrile episodes and improved oral intake. Nutritional rehabilitation was intensified through a high-protein diet and oral supplements. Calcium Carbonate 500 mg with Vitamin D3 250 IU twice daily was initiated to prevent corticosteroid-induced bone loss. Laboratory investigations showed gradual recovery of hematological parameters.

Week 4 : The patient continued Dexamethasone 5 mg/m²/day orally and received Etoposide 150 mg/m² IV on Day 25. Fever completely resolved during this week, and the patient reported significant improvement in strength and appetite. Supportive medications including Pantoprazole 40 mg once daily, Fluconazole 200 mg once daily, Trimethoprim-Sulfamethoxazole prophylaxis, and calcium-vitamin D supplementation were continued. Repeat laboratory tests demonstrated improving hemoglobin, leukocyte count, platelet count, and declining ferritin levels.

Week 5: Dexamethasone was further tapered to 2.5 mg/m²/day orally once daily, and Etoposide 150 mg/m² IV was administered on Day 32. The patient remained afebrile and ambulatory without assistance. Nutritional supplementation and adequate hydration were maintained. Regular monitoring showed continued reduction in ferritin and triglyceride levels with improvement in fibrinogen concentration. No transfusion support was required during this phase. Liver and renal function tests remained within acceptable limits without evidence of drug-related toxicity.

Week 6 : During week six, Dexamethasone 1.25 mg/m²/day orally once daily was continued, and the final scheduled dose of Etoposide 150 mg/m² IV was administered on Day 39. Significant hematological recovery was observed, with improving hemoglobin, normalization of white blood cell counts, and substantial platelet recovery. Infection prophylaxis with trimethoprim-sulfamethoxazole and fluconazole was maintained. The patient tolerated therapy well and reported complete resolution of constitutional symptoms, including weakness and anorexia.
Week 7 : The patient entered the recovery phase with continuation of low-dose Dexamethasone 1.25 mg/m²/day orally before planned discontinuation. No additional etoposide was required. Supportive medications including Pantoprazole 40 mg once daily, Calcium Carbonate with Vitamin D3 twice daily, and infection prophylaxis were continued. Clinical examination showed regression of hepatosplenomegaly and improved physical activity. Serial complete blood counts and biochemical investigations demonstrated sustained improvement without evidence of relapse or treatment-related complications.
Week 8 : At week eight, dexamethasone was gradually tapered and discontinued. Fluconazole was stopped following hematological recovery, while short-term trimethoprim-sulfamethoxazole prophylaxis was continued. Laboratory investigations revealed hemoglobin of 11.6 g/dL, total leukocyte count of 5.8 $\times 10^9$/L, platelet count of 210 $\times 10^9$/L, ferritin of 650 ng/mL, and normalized triglyceride levels. The patient was discharged in stable condition with advice for regular hematology follow-up, ferritin monitoring, and surveillance for disease recurrence.

OUTCOME AND FOLLOW-UP

Following introduction of therapy with dexamethasone and etoposide, the patient showed a remarkable clinical improvement. Fever completely disappeared by the second week of therapy. There was a gradual increase in the patient's appetite, vigor, and a sense of well-being. Serial investigations revealed normalizing blood cell counts, decreasing ferritin and triglyceride levels, and improving liver function markers. No life-threatening adverse effect was associated with therapy. By the 8th week of follow-up the patient had complete clinical remission and was well on follow up without any signs and symptoms. No evidence of relapse, recurrent cytopenias, or organ dysfunction were observed in the subsequent 3 months.

DISCUSSION

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal hyperinflammatory syndrome that often presents with nonspecific symptoms such as persistent fever, fatigue, weight loss, and pancytopenia, making early diagnosis difficult. In the present case, prolonged fever and cytopenias initially raised suspicion for severe infection, tuberculosis, or hematological malignancy. Similar diagnostic challenges have been reported in adult HLH cases where patients underwent extensive investigations before the correct diagnosis was established. The absence of specific clinical features frequently delays recognition, allowing disease progression and increasing mortality risk. Our patient's presentation closely resembled the cases described by Hicks et al. and a recent adult HLH case series, both highlighting that persistent fever with unexplained cytopenias should prompt consideration of HLH in the differential diagnosis.[11,12]
A notable feature of the current case was markedly elevated serum ferritin (18,500 ng/mL), accompanied by hypertriglyceridemia and hypofibrinogenemia. Hyperferritinemia is considered one of the most valuable laboratory clues for HLH and reflects excessive macrophage activation and cytokine release. Similar findings have been emphasized in several studies demonstrating that extremely elevated ferritin levels strongly support the diagnosis of HLH when interpreted alongside clinical findings. Our patient's ferritin concentration exceeded levels commonly associated with severe inflammatory disorders and paralleled reports in the literature where ferritin served as an important trigger for further HLH evaluation. The combination of hyperferritinemia and cytopenias in our case reinforced the suspicion of HLH and prompted bone marrow examination, leading to definitive diagnosis.[13,14]
Bone marrow aspiration in our patient demonstrated prominent hemophagocytosis, which, together with fulfillment of multiple HLH-2004 criteria, confirmed the diagnosis. Although hemophagocytosis is not exclusively seen in HLH, its presence remains an important supportive finding when correlated with clinical and laboratory abnormalities. Similar observations were reported in adult HLH case reports and institutional case series where bone marrow examination played a crucial role in establishing the diagnosis after exclusion of infectious and malignant conditions. Our patient showed characteristic macrophage-mediated phagocytosis of erythrocytes, leukocytes, and platelets, explaining the severe pancytopenia observed at presentation. These findings underscore the importance of early bone marrow evaluation in patients with unexplained fever, splenomegaly, and cytopenias.[15,16]
Early initiation of dexamethasone and etoposide-based therapy resulted in complete clinical remission in our patient, with resolution of fever, recovery of blood counts, and marked reduction in ferritin levels. This favorable outcome highlights the importance of prompt recognition and treatment before irreversible organ damage develops. Similar therapeutic success has been documented in previous reports where timely administration of immunosuppressive therapy significantly improved survival. Conversely, delayed diagnosis has been associated with poor outcomes and increased mortality. The present case reinforces the need for heightened physician awareness of HLH in adults presenting with persistent fever and pancytopenia. Early application of HLH diagnostic criteria and rapid initiation of treatment remain critical determinants of prognosis and long-term recovery.[17,18]

CONCLUSION

Hemophagocytic lymphohistiocytosis is a rare but life-threatening hyperinflammatory syndrome that can present with nonspecific manifestations such as persistent fever, pancytopenia, and hepatosplenomegaly, often leading to delayed diagnosis. This case highlights the importance of maintaining a high index of suspicion in patients with unexplained

cytopenias and markedly elevated inflammatory markers, particularly serum ferritin. Early application of HLH diagnostic criteria, prompt bone marrow evaluation, and timely initiation of dexamethasone and etoposide-based therapy were crucial in achieving favorable clinical outcomes. Increased awareness among clinicians regarding the diverse presentations of HLH may facilitate earlier diagnosis, reduce morbidity and mortality, and improve long-term patient prognosis.

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