CASE REPORT

An Unusual HLH Presentation: The Diagnostic Journey of a Factory Worker- A Case Report

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ABSTRACT

Introduction: Hemophagocytic Lymphohistiocytosis (HLH)is a rare but life-threatening syndrome of excessive immune activation, characterized by hyperinflammation due to uncontrolled activation of cytotoxic T cells, natural killer (NK) cells, and macrophages. "This results in widespread tissue damage and multi-organ dysfunction. HLH can be classified into two main types: primary (familial) HLH, which is caused by genetic mutations affecting immune regulation, and secondary HLH, which is triggered by infections, malignancies, autoimmune diseases, or other inflammatory conditions.

Case Presentation: A 37-year-old sugarcane factory worker presented with a high-grade fever for 30 days, relieved temporarily by paracetamol. He experienced weight loss, loss of appetite, and muscle pain. Two weeks before admission, he developed jaundice without vomiting, abdominal pain, or dark urine. He also noticed a painless swelling on the left side of his neck. He had no cough, breathlessness, or urinary symptoms. Despite multiple hospital visits and antibiotic treatment, his symptoms persisted. Blood tests showed pancytopenia with worsening anemia (Hb 5.8), elevated liver enzymes, direct hyperbilirubinemia, high LDH (1156), ESR (106), and extremely elevated ferritin (29,259). Infectious causes such as dengue, malaria, brucella, and leptospirosis were ruled out. Autoimmune screening was negative. CT abdomen showed hepatosplenomegaly with splenic hypodensities. 2D echocardiography was normal. On admission, he was febrile and tachycardic but stable, with hepatosplenomegaly and cervical lymphadenopathy. Bone marrow biopsy confirmed Hemophagocytic Lymphohistiocytosis (HLH). He was treated with high-dose dexamethasone along with broad-spectrum antibiotics and antifungals. His fever, jaundice, and blood counts improved, and his lymphadenopathy resolved. He also received blood transfusions for severe anemia. Currently, he is on a tapering dose of steroids and remains asymptomatic.

Conclusion: This case highlights the diagnostic complexity of Hemophagocytic Lymphohistiocytosis (HLH), a rare and potentially fatal condition that often presents with nonspecific symptoms mimicking other infectious or inflammatory disorders. Persistent fever, jaundice, pancytopenia, and hepatosplenomegaly, along with markedly elevated ferritin levels, should raise suspicion for HLH, especially when standard treatments fail to show improvement". Early diagnosis through timely bone marrow evaluation and prompt initiation of immunosuppressive therapy with corticosteroids can significantly improve outcomes. This case underscores the importance of maintaining a high index of suspicion for HLH in patients with prolonged, unexplained febrile illness and multi-system involvement.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening hyperinflammatory syndrome characterized by excessive immune activation and dysregulated cytokine release (1). It results from uncontrolled proliferation and activation of cytotoxic T lymphocytes, natural killer (NK) cells, and macrophages, leading to a cytokine storm and widespread tissue damage. "Although uncommon, HLH carries a high mortality rate if not recognized and treated promptly (2). The condition is increasingly being identified in adults due to improved diagnostic awareness and availability of advanced laboratory investigations (3).

HLH is broadly classified into primary (familial) and secondary (acquired) forms. Primary HLH is associated with genetic mutations affecting cytotoxic function, typically presenting in infancy or early childhood (4). In

contrast, secondary HLH occurs due to various triggers such as infections (especially viral infections like Epstein–Barr virus), malignancies (particularly lymphomas), autoimmune diseases, and other inflammatory conditions (5). In adults, secondary HLH is more common and often poses a diagnostic challenge due to its heterogeneous presentation and overlap with other systemic illnesses (6).

The pathophysiology of HLH involves impaired cytotoxic function of NK cells and CD8+ T cells, leading to persistent activation of macrophages and excessive production of pro-inflammatory cytokines such as interferon-gamma, tumor necrosis factor-alpha, and interleukins (7). This hypercytokinemia results in clinical features such as prolonged fever, hepatosplenomegaly, cytopenias, liver dysfunction, coagulopathy, and multi-organ failure (8). Hemophagocytosis, the hallmark feature seen on bone marrow or tissue biopsy, represents activated macrophages engulfing blood cells, although its absence does not exclude the diagnosis (9).

Diagnosing HLH remains challenging due to its nonspecific clinical features and similarity to sepsis, systemic infections, and autoimmune disorders (10). The HLH-2004 diagnostic criteria are commonly used and include a combination of clinical, laboratory, and histopathological findings such as fever, splenomegaly, cytopenias, hypertriglyceridemia or hypofibrinogenemia, elevated ferritin, decreased NK cell activity, elevated soluble CD25, and evidence of hemophagocytosis (11,12). Among these, markedly elevated serum ferritin is considered a key diagnostic clue, especially in the appropriate clinical context (13).

Early recognition and prompt initiation of treatment are critical to improving outcomes in HLH. The mainstay of therapy includes immunosuppressive and cytotoxic agents such as corticosteroids, etoposide, and cyclosporine, aimed at controlling the hyperinflammatory response (14). In secondary HLH, management of the underlying trigger is equally important. Despite advances in treatment, HLH continues to be associated with significant morbidity and mortality, particularly when diagnosis is delayed (15).

Given its rarity and protean manifestations, HLH often remains underdiagnosed or misdiagnosed, especially in resource-limited settings". This case report highlights the diagnostic challenges and clinical course of HLH in an adult patient, emphasizing the importance of maintaining a high index of suspicion in patients presenting with prolonged fever, cytopenias, and multi-organ involvement.

CASE PRESENTATION

Patient Information: A 37-year-old male, employed as a sugarcane factory worker, presented to the hospital with a prolonged history of febrile illness and systemic complaints. "He had no known history of diabetes mellitus, hypertension, tuberculosis, or any other chronic illness. There was no history of prior hospitalizations, blood transfusions, or long-term medication use. He denied any history of alcohol abuse, smoking, or exposure to toxins. There was no significant family history of hematological disorders or autoimmune diseases. His occupational exposure did not reveal any specific risk factors for zoonotic or occupational infections.

Presenting Complaints: The patient presented with a chief complaint of high-grade fever for 30 days. The fever was intermittent in nature, not associated with chills or rigors, and was temporarily relieved by antipyretics such as paracetamol. Over the course of illness, he developed progressive generalized weakness, marked loss of appetite, and significant unintentional weight loss. He also complained of diffuse muscle pain, which further contributed to his functional limitation. Approximately two weeks prior to admission, he noticed yellowish discoloration of the eyes and skin, which was not associated with pruritus, abdominal pain, vomiting, or changes in urine or stool color. In addition, he reported a painless swelling on the left side of his neck, which gradually increased in size. There were no associated symptoms such as cough, hemoptysis, breathlessness, chest pain, urinary complaints, or bleeding tendencies.

History of Present Illness: The patient had initially sought medical care at local healthcare facilities, where he was treated empirically with multiple courses of antibiotics for presumed infectious etiologies. However, his symptoms persisted and progressively worsened despite treatment. No definitive diagnosis was established during these visits. The persistence of fever along with constitutional symptoms and jaundice prompted further evaluation at a tertiary care center. There was no history suggestive of autoimmune disease such as joint pains, rashes, or photosensitivity. There were also no symptoms suggestive of malignancy such as night sweats or localized pain apart from the cervical swelling.

Clinical Examination: On presentation, the patient appeared ill and cachectic. He was febrile with a recorded temperature of 102°F and tachycardic, although his blood pressure and oxygen saturation were within normal limits, indicating hemodynamic stability. General physical examination revealed marked pallor and icterus. There was no evidence of cyanosis, clubbing, edema, or bleeding manifestations such as petechiae or purpura. Examination of the lymphatic system revealed a non-tender, firm, mobile cervical lymph node on the left side. Abdominal examination demonstrated hepatosplenomegaly, with the liver palpable below the right costal margin and the spleen enlarged and palpable. There was no ascites. Cardiovascular and respiratory system examinations were unremarkable, and neurological examination did

not reveal any focal deficits.

Laboratory Investigations: Baseline hematological investigations revealed pancytopenia, characterized by severe anemia with hemoglobin of 5.8 g/dL, leukopenia, and thrombocytopenia. Peripheral smear examination did not show any abnormal cells suggestive of hematological malignancy. Liver function tests were deranged, showing elevated transaminases and significant direct hyperbilirubinemia, indicating hepatic involvement. Serum lactate dehydrogenase (LDH) was markedly elevated at 1156 U/L, reflecting high cellular turnover and tissue damage. The erythrocyte sedimentation rate (ESR) was significantly raised at 106 mm/hr, indicating an ongoing inflammatory process. Notably, serum ferritin levels were extremely elevated at 29,259 ng/mL, which served as a crucial diagnostic clue. Additional investigations to identify infectious etiologies, including serological tests for dengue, malaria, brucellosis, and leptospirosis, were all negative. Blood cultures did not yield any growth. Autoimmune screening, including antinuclear antibodies and other relevant markers, was also negative, thereby reducing the likelihood of an autoimmune cause.

Radiological and Ancillary Investigations: Imaging studies were performed to evaluate the extent of systemic involvement. Contrast-enhanced computed tomography (CT) of the abdomen revealed hepatosplenomegaly along with multiple hypodense lesions in the spleen, suggestive of an infiltrative or inflammatory process. No focal hepatic lesions or lymphadenopathy were noted in the abdomen. A two-dimensional echocardiogram was performed to rule out cardiac involvement or infective endocarditis and was found to be normal. Chest imaging did not reveal any abnormalities, thereby excluding pulmonary pathology.

Diagnostic Workup: Given the constellation of clinical features, including prolonged fever, pancytopenia, hepatosplenomegaly, hyperferritinemia, and lack of response to conventional antibiotic therapy, a strong suspicion of Hemophagocytic Lymphohistiocytosis (HLH) was raised. The patient fulfilled several components of the HLH diagnostic criteria. To confirm the diagnosis, a bone marrow aspiration and biopsy were performed. Histopathological examination revealed the presence of activated macrophages engulfing erythrocytes, leukocytes, and platelets, consistent with hemophagocytosis. These findings confirmed the diagnosis of HLH.

Treatment and Clinical Course: Following confirmation of the diagnosis, the patient was initiated on high-dose intravenous dexamethasone as part of the standard immunosuppressive therapy aimed at controlling the hyperinflammatory state. Considering the possibility of an underlying or superimposed infection, broad-spectrum intravenous antibiotics and antifungal agents were also administered empirically. Supportive management included transfusion of packed red blood cells to correct severe anemia and maintain hemodynamic stability. Close monitoring of vital parameters, blood counts, liver function, and inflammatory markers was carried out throughout the hospital stay. Over the subsequent days, the patient showed marked clinical improvement. His fever subsided, jaundice gradually resolved, appetite improved, and his energy levels increased. Serial laboratory investigations demonstrated improvement in hematological parameters and a downward trend in inflammatory markers, including ferritin levels. The cervical lymphadenopathy also regressed significantly.

Follow-up and Outcome: The patient was discharged in a stable condition with advice for regular follow-up". He was prescribed a tapering regimen of oral corticosteroids to prevent relapse. On follow-up visits, he remained asymptomatic, with no recurrence of fever or systemic symptoms. Hematological and biochemical parameters continued to remain within normal limits, indicating sustained remission. The favorable response to therapy highlights the importance of early recognition and timely intervention in cases of HLH.

DISCUSSION

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon but life-threatening hyperinflammatory condition that often presents with nonspecific clinical features, making early diagnosis challenging. "In the present case, the patient exhibited prolonged fever, pancytopenia, hepatosplenomegaly, and markedly elevated ferritin levels, which are consistent with the classical clinical spectrum described by Konkol et al. (2025) and Khan et al. (2025)(1,2). These studies emphasize that HLH frequently mimics severe infections or sepsis, leading to diagnostic delays, as was observed in this patient who received multiple courses of antibiotics without improvement.

The pathophysiological basis of HLH involves uncontrolled activation of cytotoxic T cells and macrophages, resulting in a cytokine storm and multi-organ dysfunction. Mukherjee and Kumar (2025) highlighted the role of impaired cytotoxic pathways in perpetuating this hyperinflammatory state, which correlates with the severe clinical presentation seen in the current case (7). Similarly, Wu et al. (2024) described the molecular mechanisms underlying HLH and emphasized the importance of targeted therapeutic strategies aimed at modulating immune dysregulation (3). The favorable response of the present patient to corticosteroid therapy aligns with these mechanistic insights, as immunosuppression remains the cornerstone of treatment.

Distinguishing between primary and secondary HLH is crucial, particularly in adult patients. Öztürk et al. (2026) reported that primary HLH is typically seen in pediatric populations with genetic mutations, whereas secondary HLH, as in the present case, is more commonly

associated with infections, malignancies, or inflammatory conditions (4). Dziedzic et al. (2025) further demonstrated that secondary HLH in adults often presents with heterogeneous triggers and varied clinical manifestations, contributing to diagnostic complexity (6). Although no definitive trigger was identified in this patient, the clinical course was consistent with secondary HLH.

One of the key diagnostic challenges in HLH is its overlap with other critical illnesses. Thomas et al. (2016) described HLH as an "elusive syndrome," highlighting the difficulty in differentiating it from sepsis and other inflammatory disorders. Queffeulou et al. (2025) also emphasized its underdiagnosis in critically ill patients due to nonspecific presentations (12). In the present case, extensive evaluation ruled out common infectious and autoimmune causes, reinforcing the importance of considering HLH in patients with persistent symptoms despite standard treatment.

Hyperferritinemia is a significant diagnostic marker in HLH. Moore et al. (2013) demonstrated that markedly elevated ferritin levels are strongly associated with HLH and can aid in early recognition (13). The extremely elevated ferritin level in this patient (29,259 ng/mL) was a crucial clue that prompted further diagnostic evaluation. La Rosée and La Rosée (2024) further highlighted advancements in HLH diagnostics, emphasizing the importance of integrating clinical and laboratory criteria to improve diagnostic accuracy (11).

Management of HLH requires prompt initiation of immunosuppressive therapy along with supportive care. Salunke et al. (2019) and Hines et al. (2018) emphasized the role of corticosteroids as first-line therapy, particularly in stabilizing patients and controlling the hyperinflammatory response (14,15). The present case demonstrated significant clinical improvement following initiation of high-dose dexamethasone, along with supportive measures such as blood transfusions and antimicrobial coverage.

Additionally, secondary HLH has been reported in association with various inflammatory conditions, as highlighted by Boccucci et al. (2025), further supporting the need for a broad differential diagnosis (8). Carducci et al. (2025) also described atypical presentations of HLH with unusual organ involvement, underscoring the variability in clinical manifestations, which parallels the atypical features seen in the present case (10).

Overall, this case reinforces existing literature that HLH remains a diagnostic challenge due to its nonspecific presentation and overlap with other conditions". Early recognition based on clinical suspicion, supported by laboratory findings such as hyperferritinemia, and timely confirmation through bone marrow examination are critical. Prompt initiation of appropriate therapy can lead to favorable outcomes, as demonstrated in this patient.

CONCLUSION

This case highlights the clinical complexity and diagnostic challenges of Hemophagocytic Lymphohistiocytosis (HLH), particularly in adult patients presenting with nonspecific symptoms. The patient's prolonged fever, pancytopenia, hepatosplenomegaly, and markedly elevated ferritin closely align with classical features described in existing literature. However, initial overlap with infectious conditions led to delayed diagnosis, emphasizing the importance of early suspicion. The present study reinforces that HLH should be considered in patients with persistent febrile illness unresponsive to standard therapy. Timely bone marrow examination played a crucial role in confirming the diagnosis. Early initiation of corticosteroid therapy resulted in significant clinical and laboratory improvement, underscoring the effectiveness of prompt immunosuppressive management. This case supports existing evidence that early recognition and intervention are key determinants of outcome. Maintaining a high index of suspicion and adopting a systematic diagnostic approach can significantly reduce morbidity and mortality associated with this potentially fatal condition.

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