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HLH IN DISGUISE: A RARE BUT FATAL HYPERINFLAMMATORY SYNDROME IN AN ADULT MALE

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ABSTRACT
Hemophagocytic lymphohistiocytosis (HLH) is an uncommon and rapidly progressive hyperinflammatory syndrome that frequently mimics sepsis or hematologic malignancy, leading to delays in diagnosis. We report a 63-year-old male with bullous pemphigoid on chronic corticosteroid therapy and long-standing type 2 diabetes mellitus who presented with persistent high-grade fever, progressive cytopenias, altered sensorium, and hepatosplenomegaly. Further investigations revealed marked hyperferritinaemia, hypertriglyceridaemia, transaminitis, and hypofibrinogenaemia. Infectious and autoimmune causes were excluded after extensive evaluation. Bone marrow examination demonstrated hemophagocytosis with granulomatous inflammation, confirming HLH. The patient was managed with high-dose corticosteroids, intravenous immunoglobulin (IVIG), broad-spectrum antibiotics, and intensive supportive care. Over the following weeks, his inflammatory markers progressively improved, sensorium normalized, and cytopenias began to recover. He was discharged in a stable condition with scheduled outpatient follow-up. This case emphasizes the diagnostic complexity of adult-onset HLH in immunocompromised individuals and highlights the value of early recognition and timely immunomodulatory therapy in improving clinical outcomes.

KEYWORDS: Hemophagocytic lymphohistiocytosis, natural killer cells, cytotoxic T lymphocytes, cytokine, inflammation

INTRODUCTION
Hemophagocytic lymphohistiocytosis (HLH) is an aggressive hyperinflammatory syndrome marked by uncontrolled immune activation and rapidly progressive systemic inflammation. Initially considered a familial disorder of infancy, its recognition in adults has increased over recent decades due to improved diagnostic awareness and expanding identification of triggers (1). Adult-onset HLH is frequently underdiagnosed as its early manifestations resemble sepsis, acute hepatic dysfunction, or hematologic malignancy, resulting in delayed treatment and increased morbidity. Reports from Indian tertiary centres emphasize that adult HLH is a serious and potentially fatal condition, often presenting with fulminant clinical deterioration (1).
At a pathophysiological level, HLH arises from impaired cytotoxic activity of natural killer (NK) cells and cytotoxic T lymphocytes, leading to persistent antigenic stimulation, macrophage overactivation, and a cytokine storm dominated by interferon-γ, tumour necrosis factor-α, and interleukin-6 (2). This uncontrolled immune activation results in excessive macrophage-mediated phagocytosis of hematopoietic cells and widespread tissue inflammation . These mechanisms produce the characteristic clinical triad of fever, cytopenias, and organomegaly, along with hyperferritinaemia, hypertriglyceridaemia, and hypofibrinogenemia. In adults, these abnormalities evolve rapidly and may be mistakenly attributed to infections or autoimmune flare-ups, particularly in individuals with chronic illnesses (2). The absence of a single pathognomonic feature and the overlap with sepsis, macrophage activation syndrome, and malignancy contribute to substantial diagnostic difficulty.
A systematic review of adult HLH cases demonstrated frequent diagnostic delays due to nonspecific clinical presentations (3). Many patients initially exhibit features suggestive of hematologic malignancy or overwhelming infection, making it essential for clinicians to maintain a high index of suspicion in adults presenting with persistent fever, refractory cytopenias, transaminitis, or unexplained multiorgan dysfunction. Early recognition is critical, as HLH can rapidly progress into irreversible immune dysregulation, and timely immunomodulatory therapy significantly improves outcomes (3).
Understanding HLH in adults also requires consideration of its diverse triggers, which differ from pediatric forms. While familial HLH is genetically mediated, adult HLH is commonly associated with infections, autoimmune diseases, or malignancies. Failure of cytotoxic lymphocytes to eliminate activated antigen-presenting cells results in a self-amplifying inflammatory cycle resistant to physiological regulation (4). This mechanism explains the profound elevations in serum ferritin, hepatic dysfunction, coagulopathy, and neurological manifestations seen in

many adult cases, and underscores the necessity of immune-directed therapy rather than antimicrobial treatment alone.
Growing awareness of adult HLH is evident in recent cohorts. Zhou et al. identified fever, hepatosplenomegaly, pancytopenia, and liver dysfunction as predominant features, with hyperferritinaemia serving as a strong diagnostic marker (6). These findings highlight the aggressive nature of the syndrome and the impact of delayed diagnosis.

Case presentation:
A 63-year-old male with a history of bullous pemphigoid on chronic systemic corticosteroids and long-standing type 2 diabetes mellitus presented to the emergency department with a ten-day history of continuous high-grade fever. The fever, initially intermittent, became persistent and was associated with malaise, reduced appetite and two episodes of non-projectile vomiting. Over the preceding three days, his family reported increasing drowsiness, reduced verbal output, and fluctuating level of consciousness.
On examination, the patient appeared acutely ill, febrile and disoriented. Pallor and dehydration were noted. There was no icterus or palpable lymphadenopathy. Skin examination showed healed hyperpigmented patches corresponding to prior bullous lesions. Abdominal examination revealed tender hepatosplenomegaly, with the liver palpable 4 cm below the right costal margin and the spleen 2 cm below the left costal margin. Cardiovascular examination showed tachycardia with normal heart sounds, and bilateral basal crepitations were heard on respiratory auscultation. His Glasgow Coma Scale score was 13/15 without focal neurological deficits. Despite systemic illness, circulatory status remained preserved without vasopressor support.
Initial laboratory evaluation showed pancytopenia, markedly elevated hepatic enzymes, deranged liver function tests, renal dysfunction, and raised inflammatory markers. Serum ferritin exceeded 15,000 ng/mL, triglycerides were 398 mg/dL and fibrinogen was reduced to 128 mg/dL. Lactate dehydrogenase was >2,500 U/L, and C-reactive protein and erythrocyte sedimentation rate were significantly raised. Mild hyponatremia and uncontrolled hyperglycaemia were also present. Neutrophilic leukocytosis was notably absent. Infectious evaluation—including blood cultures, urine cultures, dengue serology, malarial studies, scrub typhus IgM, leptospira serology and viral markers (HIV, hepatitis B, hepatitis C and SARS-CoV-2)—was negative. and evaluation for tuberculosis including sputum studies and imaging—was negative, effectively ruling out tuberculosis. Autoimmune workup including antinuclear antibody and anti–double-stranded DNA was non-reactive, with normal complement levels. Radiological assessment included a chest radiograph showing mild interstitial infiltrates, and abdominal ultrasonography confirming hepatosplenomegaly without ascites. Contrast-enhanced computed tomography of the abdomen and thorax revealed mild hepatosplenomegaly and early lower-lobe consolidation without lymphadenopathy or malignancy.
Given the combination of persistent fever, cytopenias, hyperferritinaemia and multiorgan involvement, HLH was strongly suspected. Bone marrow aspiration and biopsy performed on day five demonstrated normocellular marrow with prominent hemophagocytosis involving erythroid and myeloid precursors, along with granulomatous inflammation. There was no evidence of hematologic malignancy or fungal infection. These findings, together with the clinical and biochemical abnormalities, fulfilled HLH-2004 diagnostic criteria and confirmed the diagnosis.
The patient was treated with intravenous immunoglobulin at 1 g/kg and escalation of systemic corticosteroids. Broad-spectrum antibiotics were continued until infectious causes were definitively excluded. Supportive measures included strict glycaemic control, fluid management, thromboprophylaxis and close monitoring in a high-dependency unit.
Over the following days, the patient showed gradual clinical improvement. His fever subsided, sensorium improved and respiratory distress settled with supportive measures. Inflammatory markers, ferritin levels and liver enzymes progressively declined, while blood counts began to recover. Repeat imaging showed resolution of lower-lobe changes. By the end of the third week, his organ function had stabilized, and he no longer required oxygen support. He was discharged in stable condition on tapering corticosteroids, advised regular follow-up and monitoring for recurrence.
The final diagnosis was hemophagocytic lymphohistiocytosis secondary to chronic immunosuppression in an elderly male, showing favourable clinical response to timely immunomodulatory therapy and supportive care.

TABLE 1. Vital Signs and Laboratory Parameters of the Patient on Admission

S. No	Parameter	Result
1	Temperature	39.1°C
2	Heart rate	118/min
3	Blood pressure	96/62 mmHg

4	Respiratory rate	28/min
5	SpO_2 (room air)	92%
6	Hemoglobin	8.2 g/dL
7	Total leukocyte count	2,100/µL
8	Platelet count	52,000/µL
9	AST	426 U/L
10	ALT	389 U/L
11	Total bilirubin	1.8 mg/dL
12	Urea	76 mg/dL
13	Creatinine	1.9 mg/dL
14	Ferritin	>15,000 ng/mL
15	Triglycerides	398 mg/dL
16	Fibrinogen	128 mg/dL
17	LDH	>2,500 U/L
18	C-reactive protein (CRP)	189 mg/L
19	Erythrocyte sedimentation rate (ESR)	74 mm/hr
20	Serum sodium	129 mmol/L
21	Random blood glucose	260–340 mg/dL

DISCUSSION

The present case illustrates the diagnostic complexity of secondary hemophagocytic lymphohistiocytosis (HLH) in adults, particularly in individuals with underlying immunosuppression. The patient presented with persistent high-grade fever, pancytopenia, hepatosplenomegaly, transaminitis, hypertriglyceridaemia and markedly elevated ferritin—clinical and laboratory features that strongly suggested HLH. His initial lack of response to broad-spectrum antimicrobials further supported a hyperinflammatory rather than infectious etiology.

At a pathophysiological level, HLH represents a state of uncontrolled immune activation resulting from defective cytotoxic function of natural killer cells and cytotoxic T lymphocytes. This impairment leads to persistent activation of macrophages and T cells, culminating in excessive cytokine release, commonly referred to as a "cytokine storm." Elevated levels of pro-inflammatory cytokines such as interferon-γ, tumour necrosis factor-α, and interleukins drive systemic hyperinflammation, tissue injury, and multiorgan dysfunction, which clinically mimics severe sepsis and contributes to diagnostic delay.

Comparable diagnostic determinants have been reported by Selvam et al., who observed that persistent fever, cytopenias and profoundly elevated ferritin were key predictors of HLH in adults with scrub typhus (7). Although our patient had no identifiable infectious trigger, his constellation of severe inflammation mirrored the pattern described in their study, emphasising the importance of maintaining high clinical suspicion when inflammatory markers are disproportionately elevated.

The broader phenotypic variability of adult HLH was described by Jumić et al., who noted that multiorgan involvement—particularly cytopenias and hepatic dysfunction—was present irrespective of the underlying trigger (8). Our patient's clinical profile was consistent with these findings. Their emphasis on delayed diagnosis contributing to adverse outcomes highlights the need for early recognition and timely initiation of immunomodulatory therapy, which was achieved in this case.

Rabadão et al. reported extensive hemophagocytosis with neurological manifestations in an immunocompetent adult with HLH, demonstrating that bone marrow evaluation remains crucial for diagnostic confirmation (9). Similarly, bone marrow analysis in our patient revealed prominent hemophagocytosis with granulomatous inflammation, supporting the diagnosis and guiding early treatment. However, unlike their patient who showed early improvement, our patient's chronic corticosteroid exposure may have modified the initial presentation, delaying recognition.

The Histiocyte Society blueprint described by Meyer et al. highlights that elderly adults with HLH often exhibit complex immune dysregulation and atypical presentations, necessitating early clinical suspicion to prevent progression to irreversible organ dysfunction (10). These observations align with our patient's clinical trajectory, wherein prompt initiation of intravenous immunoglobulin and escalation of corticosteroids resulted in gradual improvement in fever, sensorium and inflammatory markers.

Harrison et al. demonstrated that hepatic dysfunction and sepsis-like physiology predict poorer outcomes in adult HLH (11). Although our patient exhibited several of these risk markers at presentation, early recognition and targeted immunomodulation contributed to stabilisation of organ function and recovery, underscoring the value of timely intervention even in high-risk individuals.

HLH remains under-recognised in adult populations, as highlighted in an Indian multicentre report where many patients initially received prolonged antimicrobial therapy for presumed sepsis (12). This pattern reflects the early phase of our case, emphasising that clinicians must consider HLH when standard therapy fails and inflammation is disproportionate.

Ferritin continues to be one of the most reliable biomarkers for HLH diagnosis. Sarangi et al. identified extremely elevated ferritin as a distinguishing feature of hyperinflammatory states compared to other febrile illnesses (13). The ferritin level exceeding 15,000 ng/mL in our patient supported the diagnosis and correlated with disease severity. With therapy, ferritin levels progressively declined, paralleling clinical improvement.

HLH associated with immune dysregulation has been described by Park et al., who reported that such patients often experience more severe disease but respond well to immunosuppressive therapy when instituted promptly (14). Our patient's chronic steroid use for bullous pemphigoid likely contributed to immune imbalance; however, his response to IVIG and corticosteroid escalation was favourable.

Ramos-Casals et al. highlighted the high mortality associated with delayed HLH diagnosis, particularly when respiratory compromise occurs (15). Unlike the severe outcomes often reported, our patient showed clinical improvement with early targeted therapy and supportive measures, eventually achieving stabilisation and being discharged with follow-up.

Collectively, the available literature reinforces that adult HLH requires high clinical suspicion, early diagnostic evaluation and prompt immunomodulatory therapy. The present case aligns with these principles, demonstrating favourable clinical response, recovery of hematologic parameters and stabilisation of organ function following timely treatment.

CONCLUSION

Adult-onset hemophagocytic lymphohistiocytosis remains a significant diagnostic challenge, particularly in individuals with underlying immune dysregulation or chronic corticosteroid exposure. This case highlights the importance of considering HLH in adults who present with persistent fever, cytopenias, organomegaly and disproportionately elevated inflammatory markers, especially when they do not improve with standard antimicrobial therapy. Bone marrow evaluation played a pivotal role in establishing the diagnosis, reaffirming its value in complex febrile illnesses accompanied by pancytopenia.

Early recognition and timely initiation of immunomodulatory therapy were central to the favourable outcome in this patient. Intravenous immunoglobulin, escalation of corticosteroids and supportive care resulted in progressive clinical and biochemical improvement, with recovery of hematologic parameters and stabilisation of organ function. The patient was discharged in a stable condition with scheduled follow-up, underscoring that early, targeted intervention can significantly modify the disease course even in high-risk individuals.

This case reinforces the need for heightened clinical vigilance, structured diagnostic pathways and prompt initiation of therapy to improve outcomes in adult HLH, particularly in immunocompromised populations.

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