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HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: AN UNCOMMON PRESENTATION IN SYSTEMIC LUPUS ERYTHEMATOSUS AND ACUTE LEUKAEMIA

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ABSTRACT

Introduction: Haemophagocytic lymphohistiocytosis (HLH) is a rare and potentially life-threatening hyperinflammatory syndrome, characterised by uncontrolled activation of cytotoxic T lymphocytes, natural killer cells and macrophages, leading to a cytokine storm and subsequent multiorgan damage. While HLH predominantly affects paediatric populations, it is increasingly recognised in adult patients, often occurring in association with malignancies, infections or autoimmune diseases.

Case description: We present two distinct adult cases of HLH. Case 1 involves a 21-year-old woman with newly diagnosed systemic lupus erythematosus (SLE), who developed macrophage activation syndrome (MAS)-associated HLH. She presented with prolonged fever, polyarthralgia, malar rash, hepatosplenomegaly, bicytopenia, hypofibrinogenaemia, hypertriglyceridaemia and elevated serum ferritin levels. Case 2 describes a 44-year-old woman with acute monoblastic leukaemia (AML-M5) and malignancy-associated HLH, who presented with fever, malaise, hepatosplenomegaly, hypofibrinogenaemia, hypertriglyceridaemia and hyperferritinaemia. An initial haematological response was achieved; however, disease progression ultimately led to fatal multiorgan failure secondary to neutropenic pancolitis caused by *Clostridioides difficile* infection.

Discussion: Both cases illustrate key clinical and pathophysiological differences in the evolution, management and outcomes of HLH, depending on the underlying cause. While both fulfilled the HLH-2024 diagnostic criteria, they exhibited markedly different responses to therapy and outcomes.

Conclusion: These cases highlight the need to suspect HLH in patients with prolonged fever, cytopaenia, organomegaly and high ferritin. Early treatment improves prognosis, especially in autoimmune HLH, where steroids are effective, while malignancy-related HLH often has poorer outcomes.

KEYWORDS

Haemophagocytic lymphohistiocytosis, systemic lupus erythematosus, acute monoblastic leukaemia, macrophage activation syndrome, hyperferritinaemia

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LEARNING POINTS

- Haemophagocytic lymphohistiocytosis (HLH) should be suspected in patients with persistent fever, cytopaenia, organomegaly and markedly elevated ferritin, particularly in the context of autoimmune diseases or haematologic malignancies.
- Early therapeutic intervention significantly improves prognosis in autoimmune-associated HLH, where corticosteroid therapy is often effective, while malignancy-driven HLH typically carries poorer outcomes despite aggressive treatment.
- A multidisciplinary approach is essential for HLH management, with treatment strategies tailored to the underlying cause rather than following a uniform protocol.

INTRODUCTION/BACKGROUND

Haemophagocytosis is a pathological condition in which activated macrophages engulf erythrocytes, leukocytes, platelets and their progenitor cells. This finding is a hallmark of HLH, caused by severe immune hyperactivation triggered by lymphocyte cytotoxicity defects, infections, malignancies, rheumatologic diseases or immunodeficiencies[1]. The term 'HLH syndrome' refers to any clinical condition that meets the established diagnostic criteria for HLH. These cases are categorised into subtypes based on underlying mechanisms, including familial forms with genetic defects, HLH associated with rheumatologic disease, malignancy, immune-activating therapies, immunodeficiency or idiopathic cases, as well as HLH mimics, which resemble HLH but have distinct pathophysiology and require different treatment approaches[1,2]. Our patients fit within the categories of macrophage activation syndrome (Case 1) and malignancy-associated HLH (Case 2), supporting the relevance of this updated framework in clinical practice. HLH is life-threatening due to its rapid progression to multisystem organ failure if not promptly diagnosed and treated with immunosuppressive therapy[3,4].

In contrast to the advances seen in paediatric patients, delayed diagnosis, missed underlying trigger conditions and non-standardised treatment protocols still result in a mortality rate of 40 to 80% among adult patients with HLH[5]. In this article, we present two distinct cases of HLH: one associated with newly diagnosed SLE in a young woman, and another with AML-M5 in a middle-aged patient. Both cases met the HLH-2024 diagnostic criteria and illustrate key differences in disease evolution, management and outcomes based on the underlying aetiology[5].

CASE DESCRIPTION

Case 1: A 21-year-old woman with a history of obesity, polycystic ovary syndrome and hypothyroidism presented with arthralgia and persistent fever (38°C) for seven days. She reported two years of progressive joint pain affecting hands, elbows, shoulders and knees. Additionally, she described confluent erythematous skin lesions on her legs, arms and face, particularly with a malar distribution, that appeared and worsened with sun exposure. She had experienced an unintentional weight loss of 45 kg, xerostomia, oral ulcers, alopecia and photosensitivity. Physical examination revealed malar rash, lymphadenopathy and hepatosplenomegaly. On admission, vital signs showed a blood pressure of 91/54 mmHg, a heart rate of 117 beats per minute, a temperature of 38.6 °C, a respiratory rate of 18 breaths per minute and an oxygen saturation of 96% on room air. These findings corresponded to a National Early Warning Score 2 of 5, indicating moderate clinical risk. Laboratory findings showed bicytopenia (Hb 76 g/l, neutropenia 0.696 $\times 10^9$/l), fibrinogen 1.5 g/l, elevated inflammatory markers (erythrocyte sedimentation rate 57 mm/h, C-reactive protein 46 mg/l), positive antinuclear antibodies (1:1,280 with a homogeneous pattern), elevated anti-dsDNA (64.5 IU/ml), low complement levels (C3: 0.37 g/l; C4: 0.07 g/l), elevated ferritin (1,057 ng/ml) and mild proteinuria (434 mg/24 h). Thoracoabdominal CT imaging revealed pathological lymphadenopathies in the axillary, clavicular, inguinal and external iliac regions, with lesser involvement in the para-aortic and internal iliac chains, along with hepatosplenomegaly. Despite initial corticosteroid therapy (1 mg/kg/day), the patient's condition deteriorated, with persistent fever, negative blood cultures, worsening cytopaenia and elevated triglycerides at 312 mg/dl. A lymph node biopsy initially raised suspicion for low-grade follicular lymphoma due to BCL-2 positivity; however, the characteristic t(14;18) translocation in B lymphocytes was not detected. The final pathology report indicated atypical follicular hyperplasia, consistent with an underlying autoimmune process. Following the exclusion of lymphoproliferative disease, disease, and having met the HLH-2024 criteria (as listed in *Table 1*), a diagnosis of MAS-HLH was established, despite the absence of haemophagocytosis in the bone marrow biopsy. An HLH Diagnostic Score (HScore), a weighted scoring system based on nine clinical and laboratory variables used to estimate the probability of HLH *(Table 2)*, was calculated at 188, corresponding a 70–80% probability of HLH[6]. Treatment was intensified with high-dose corticosteroids (1.5 mg/kg/day) and hydroxychloroquine, leading to clinical and laboratory improvement. The patient achieved a state of low disease activity (SELENA-SLEDAI ≤4) and is currently maintained on hydroxychloroquine, azathioprine and low-dose prednisone (≤5 mg/day). Initiation of belimumab is under consideration as part of long-term disease management.

Case 2: A 44-year-old woman with cerebral palsy (spastic tetraparesis), maintained a good functional status and

Feature	Criteria/cut-off
Fever	≥ 38.5°C
Splenomegaly	≥ 2 cm below costal margin
Cytopenia (at least 2 of 3 cell lines)	Haemoglobin < 90 g/l Platelets < 100 ×10^9/l Neutrophils < 1 ×10^9/l
Hypofibrinogenaemia or Hypertriglyceridaemia	Fibrinogen ≤ 1.5 g/l or triglycerides ≥ 3.0 mmol/l
Hyperferritinaemia	Ferritin ≥ 500 µg/l
Haemophagocytosis	Detected in bone marrow or other tissues
Elevated soluble IL-2 receptor α (CD25)	≥2,400 U/ml

Table 1. HLH-2024 diagnostic criteria[1]. The diagnosis of HLH is based on fulfilling ≥5 criteria.

Variable	Consideration in scoring
Fever	Presence of fever
Organomegaly	Hepatomegaly and/or splenomegaly
Immunosuppression	Known underlying immunosuppressive condition
Haemophagocytosis	Detected in bone marrow or other tissues
Cytopenia	Number and severity of cytopenia
Ferritin	Higher levels increase score
Triglycerides	Higher levels increase score
Fibrinogen	Lower levels increase score
Aspartate aminotransferase	Elevated levels

Table 2. HScore diagnostic criteria[6]. The probability of having HLH ranged from <1% with an HScore of ≤90 to >99% with an HScore of ≥250.

remained professionally active, presented with five days of high fever (39°C), general malaise, cough and right hypochondrial pain. On examination, she had impaired general condition, pallor, decreased breath sounds at the right lung base and tenderness in the right hypochondrium. On admission, vital signs showed a blood pressure of 86/52 mmHg, a heart rate of 102 beats per minute, a temperature of 38.7°C, a respiratory rate of 20 breaths per minute and an oxygen saturation of 90% on room air. These findings corresponded to a National Early Warning Score of 8, consistent with high clinical risk. Laboratory tests revealed bicytopenia (Hb 98 g/l and platelets 21 ×10^9/l), fibrinogen 1.6 g/l, elevated inflammatory markers (C-reactive protein 105 mg/l), coagulopathy (Quick 49%, D-dimer 4,757 ng/ml), liver dysfunction (aspartate aminotransferase 401 U/l, alanine transaminase 161 U/l, gamma-glutamyl transferase GGT 247 U/l, alkaline phosphatase 267 U/l, lactate dehydrogenase 1,793 U/l), hypertriglyceridaemia (347 mg/dl), hypoproteinaemia (45 g/l with normal protein electrophoresis), hypocholesterolaemia (63 mg/dl), elevated lactate (7.3 mmol/l) and ferritin of 7,571 ng/ml. Chest X-ray showed normal cardiac silhouette with bilateral pleural effusion. Abdominal CT revealed hepatomegaly with decreased density, periportal oedema and free fluid in the pelvis. Initially managed as suspected abdominal sepsis, laparoscopy revealed inflammatory ascitic fluid (negative cytology and culture), hepatosplenomegaly and mesenteric adenitis. Broad-spectrum antibiotics (aztreonam and levofloxacin) were started for abdominal and respiratory coverage. After surgical pathology was ruled out, ganciclovir was added. Further workup revealed negative blood cultures and serologies, including Paul-Bunnell test, hepatitis B surface antigen, immunoglobin M anti-hepatitis B core, anti-hepatitis A virus, anti-hepatitis C virus, anti-toxoplasma, anti-HIV and anti-cytomegalovirus. Immunological studies showed positive anti-platelet antibodies and negative antinuclear antibodies. Despite supportive care, she developed progressive clinical deterioration with metabolic acidosis, worsening bicytopenia and coagulopathy. Bone marrow aspiration revealed absence of megakaryocytes, severely decreased granulocytic series, 65% irregular cells with basophilic cytoplasm and numerous histiocytes with haemophagocytosis, suggesting AML-M5 with associated HLH. She subsequently experienced an episode

Feature	Case 1: SLE-associated HLH	Case 2: AML-associated HLH
Patient	Female, 21 years old	Female, 44 years old
Clinical manifestations	Fever, arthralgia, malar rash, lymphadenopathy, hepatosplenomegaly	Fever, malaise, right hypochondrial pain, hepatosplenomegaly, pleural effusion
Laboratory findings	• Haemoglobin: 76 g/l (↓) • Platelets: 456 ×10⁹/l (↑) • Neutrophils: 0.696 ×10⁹/l (↓) • Ferritin: 1,057 ng/ml (↑) • Triglycerides: 312 mg/dl (↑) • C-reactive protein: 46 mg/l (↑) • Fibrinogen: 1.5 g/l (↓) • Antinuclear antibodies 1:1,280 (↑) • Anti-dsDNA: (↑) • Complement components 3&4: (↓)	• Haemoglobin: 98 g/l (↓) • Platelets: 21 ×10⁹/l (↓) • Neutrophils: 5,467 ×10⁹/l (normal) • Ferritin: 7,571 ng/ml (↑) • Triglycerides: 347 mg/dl (↑) • C-reactive protein: 105 mg/l (↑) • Fibrinogen: 1.6 g/l (↓) • Antinuclear antibodies: negative • Anti-platelet antibodies: positive
Pathology findings	Lymph node biopsy: BCL-2 positive; t(14;18) negative	Bone marrow: 65% blasts with haemophagocytosis
NEWS2	5	8
HSCORE	188	249
Treatment	Corticosteroids, hydroxychloroquine, azathioprine	Antibiotics, corticosteroids, idarubicin/ cytarabine, later azacitidine
Outcome	Maintains low disease activity	Initial remission followed by relapse and death due to multiorgan failure

Table 3. Summary of two HLH cases: SLE and AML presentations.

of supraventricular tachycardia and was transferred to the ICU, where she required and mechanical ventilation. An HScore of 249, indicating a greater than 99% probability of HLH, supported the presumptive diagnosis and justified the initiation of corticosteroid therapy. A subsequent bone marrow study confirmed AML-M5 with associated haemophagocytosis, without cytogenetic abnormalities, no FMS-like tyrosine kinase 3 FLT3 duplication and wild-type nucleophosmin. Despite achieving an initial haematologic and clinical response to chemotherapy with idarubicin and cytarabine, the patient developed neutropenic pancolitis and subsequently relapsed with newly acquired cytogenetic abnormalities. Second-line therapy with azacitidine was ineffective; she ultimately died from multiorgan failure secondary to neutropenic colitis with Clostridioides difficile infection, with final diagnoses of HLH, AML-M5 and neutropenic pancolitis.

DISCUSSION

HLH is a diagnostic and therapeutic challenge with non-specific symptoms and multiple triggers including infections, malignancies and autoimmune diseases such as SLE[1]. The two cases show this complexity: one autoimmune, one malignancy-related. HLH is a medical emergency requiring early recognition and targeted treatment.

As summarised in *Table 3*, our cases demonstrate the clinical and laboratory differences between SLE-associated and AML-associated HLH, highlighting the varied presentations and outcomes that can occur with this syndrome. The comparison reveals marked hyperferritinaemia in the malignancy-associated case. SLE-associated HLH symptoms overlap with SLE flares, causing diagnostic delays[7]. SLE disease activity triggers macrophage activation syndrome, especially as an initial disease manifestation[8].

Our first case highlights the importance of considering HLH in young patients with active SLE, even in the absence of bone marrow haemophagocytosis. The outcome in this patient was excellent, suggesting that early use of corticosteroids and immunosuppressive therapy can be life-saving when HLH is identified and treated promptly.

Case 2 demonstrates the aggressive course and poor prognosis of malignancy-associated HLH, despite appropriate chemotherapy and critical care. Malignancy-triggered HLH has been associated with high mortality rates, particularly when compounded by chemotherapy-induced immunosuppression, sepsis or multiorgan failure[8]. This underlines the need for better biomarkers and targeted therapies to improve survival in malignancy-associated HLH. In Case 2, clinical and laboratory findings could reflect the underlying leukaemia. However, early improvement with chemotherapy suggested a concurrent HLH component. Both cases fulfilled HLH-2024 criteria, with elevated HScores providing diagnostic support. These tools are useful but must be interpreted with caution, given the overlap with other hyperinflammatory conditions such as sepsis and disseminated intravascular coagulation. HLH-2024 criteria were preferred over HLH-2004 due to better applicability in adults and the use of accessible markers, while excluding complex tests such as natural killer cell activity[4,6].

The Optimized HLH Inflammatory score, a tool designed to

identify malignancy-associated HLH based on ferritin and soluble interleukin-2 receptor (sCD25) levels, could not be applied in this case due to the unavailability of sCD25[9].

These cases highlight the inherent diagnostic challenge in HLH of balancing the need for high sensitivity in a rapidly fatal syndrome with the reality that many criteria are shared with severe infections and systemic inflammation.

Multidisciplinary management is crucial for timely diagnosis and tailored therapy. Future research should focus on early biomarkers, risk stratification and integrating emerging therapies into standard HLH protocols.

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