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HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AS AN INITIAL PRESENTATION OF UNDIAGNOSED SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

Background: Haemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal hyperinflammatory syndrome with multi-organ involvement. It may occur secondary to autoimmune diseases such as systemic lupus erythematosus (SLE).
Case description: This report describes an unusual case of a previously healthy 29-year-old female medical student who presented with a one-month history of recurrent fever, fatigue and significant weight loss. Initial laboratory investigations revealed pancytopaenia, hyperferritinaemia and hypertriglyceridaemia. Infectious disease workup was negative. Serological testing demonstrated positive antinuclear antibody and anti-double-stranded DNA antibodies, while bone marrow biopsy confirmed haemophagocytosis. The patient was diagnosed with secondary HLH due to SLE. During treatment in the intensive care unit, the patient developed psychosis manifested by visual hallucinations and mood swings. A diagnosis of neuropsychiatric SLE was confirmed by exclusion of other causes (e.g. steroid therapy) and the presence of non-specific white matter hyperintensities on brain magnetic resonance imaging. Combination therapy with high-dose corticosteroids, intravenous immunoglobulin and rituximab resulted in significant clinical and laboratory improvements within two weeks.
Conclusion: This case illustrates how HLH can be the initial manifestation of previously undiagnosed SLE. Hence, clinicians should maintain a high index of suspicion for underlying autoimmune disorders such as SLE when evaluating patients with HLH, as early recognition and appropriate immunosuppressive therapy are crucial for optimal outcomes.

KEYWORDS

Haemophagocytic lymphohistiocytosis, macrophage activation syndrome, systemic lupus erythematosus, neuropsychiatric SLE, hyperferritinaemia

LEARNING POINTS

- Clinicians should suspect haemophagocytic lymphohistiocytosis in patients with persistent fever and cytopaenias, especially when laboratory findings (e.g. hyperferritinaemia, hypertriglyceridaemia) do not improve with standard treatments.
- Systemic lupus erythematosus may initially present as secondary haemophagocytic lymphohistiocytosis. Integration of clinical, radiological and immunological data can aid in early differentiation.

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INTRODUCTION

Haemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory disorder characterised by a cytokine storm and multi-organ dysfunction. It is classified into two types: primary in children and secondary in adults. Primary HLH is an autosomal recessive disease that occurs due to mutations in genes modulating cytolytic roles or lymphocyte survival. Secondary HLH occurs due to infections, malignancies and rheumatological conditions such as systemic lupus erythematosus (SLE), where it is referred to as macrophage activation syndrome (MAS)[1]. Rheumatological disorders initiate an inflammatory cascade through the formation of autoantibodies and immune complexes, resulting in excessive activation of macrophages and T lymphocytes[2].

HLH is characterised by persistent fever, pancytopenia, hepatosplenomegaly, elevated ferritin and hypertriglyceridemia. These features often overlap with those of active SLE, leading to delayed diagnosis and high risk of morbidity and mortality[3]. HLH occurs in 0.9 to 4.6% of SLE cases where it typically develops later in the disease course and is rarely the initial presentation in adult patients[4]. In this report, we present a rare case that had undiagnosed SLE and presented initially with HLH.

CASE DESCRIPTION

A 29-year-old Saudi female, with no previous medical history, presented to the emergency department with a one-month history of recurrent fever and generalised fatigue. She was a medical student studying in Georgia where she initially developed fever and shortness of breath, symptoms that were also reportedly experienced by several of her colleagues at that time. During her stay in Georgia, she received multiple courses of empiric antibiotics, antivirals and antifungals without clinical improvement. Upon returning to Saudi Arabia, she presented directly from the airport with progressive symptoms including nausea, vomiting and significant unintentional weight loss (about 10 kg over one month). She reported no history of skin rashes, mucosal ulcers or arthralgias. Her family medical history was irrelevant.

On admission, vital signs indicated low-grade fever (37.7°C; normal < 37.5°C), tachycardia (116 beats/min; normal 60–100) and hypotension. Physical examination demonstrated cachexia and non-tender lymphadenopathy involving preauricular, cervical and axillary regions. There was no skin rash, hepatosplenomegaly, abdominal tenderness or rebound pain.

Initial laboratory investigations revealed haemoglobin at 9.3 g/dl (reference range 12–16 g/dl), a total leukocyte count of 0.98 $\times 10^9$/l (reference range 4–11 $\times 10^9$/l), an absolute neutrophil count of 0.51 $\times 10^3$/l (reference range 1.5–8 $\times 10^3$/l), and a platelet count of 138 $\times 10^9$/l (reference range 150–450 $\times 10^9$/l). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were within normal limits. Serum ferritin was markedly elevated at 3,240 ng/ml (reference range 15–150 ng/ml) and serum triglycerides were raised to 1,549 mg/dl (reference range <150 mg/dl). Serum complements 3 (C3) level was low at 41.2 mg/dl (reference range 90–180 mg/dl) while serum complement 4 (C4) level was normal. Serum lactate dehydrogenase (LDH) was elevated at 1,549 U/l (reference range 140–280 U/l). Liver function tests showed aspartate transaminase (AST) at 887 U/l and alanine transaminase (ALT) at 321 U/l (reference range <40 U/l for both). See *Table 1* for summary. Serological testing demonstrated positive antinuclear antibody (ANA) and anti-double-stranded DNA (anti-dsDNA; 100 IU/ml; normal <30 IU/ml), whereas other autoimmune markers including anti–Sjögren's-syndrome-related antigen A (anti-SSA), anti–Sjögren's-syndrome-related antigen B (anti-SSB), anti-scleroderma-70 (anti-Scl-70), anti-neutrophil cytoplasmic antibody, anti-ribonucleoprotein (anti-RNP) and anti-phospholipid antibodies were negative. Widal and Coombs tests, as well as tests for Epstein-Barr virus, brucella, leptospira, dengue virus, cytomegalovirus, human immunodeficiency virus, and hepatitis B and C viruses were negative. Blood and sputum cultures showed no growth at 48 hours and after five days.

Computed tomography (CT) imaging of the chest and abdomen revealed multiple lymphadenopathies without hepatosplenomegaly. A peripheral blood smear confirmed hypochromic anaemia with a low reticulocyte count (0.3%; reference 0.5–1.5%), agranulocytosis, moderate lymphopenia and mild thrombocytopaenia with no evidence of blasts or dysplastic changes. An axillary lymph node biopsy showed reactive hyperplasia, while a bone marrow biopsy

Laboratory investigation	Value	Reference range
Haemoglobin (g/dl)	9.3	12–16
Total leukocyte count ($\times 10^9$/l)	0.98	4–11
Absolute neutrophil count ($\times 10^3$/l)	0.51	1.5–8
Platelet count (×109/l)	138	150–450
ESR (mm/hr)	19	0–20
CRP (mg/dl)	0.4	<0.5
Serum ferritin (ng/ml)	3,240	15–150
Serum triglycerides (mg/dl)	1,549	<150
C3 (mg/dl)	41.2	90–180
C4 (mg/dl)	10.4	10–40
LDH (U/l)	1,549	140–280
AST (U/l)	887	<40
ALT (U/l)	321	<40

Table 1. Laboratory findings.

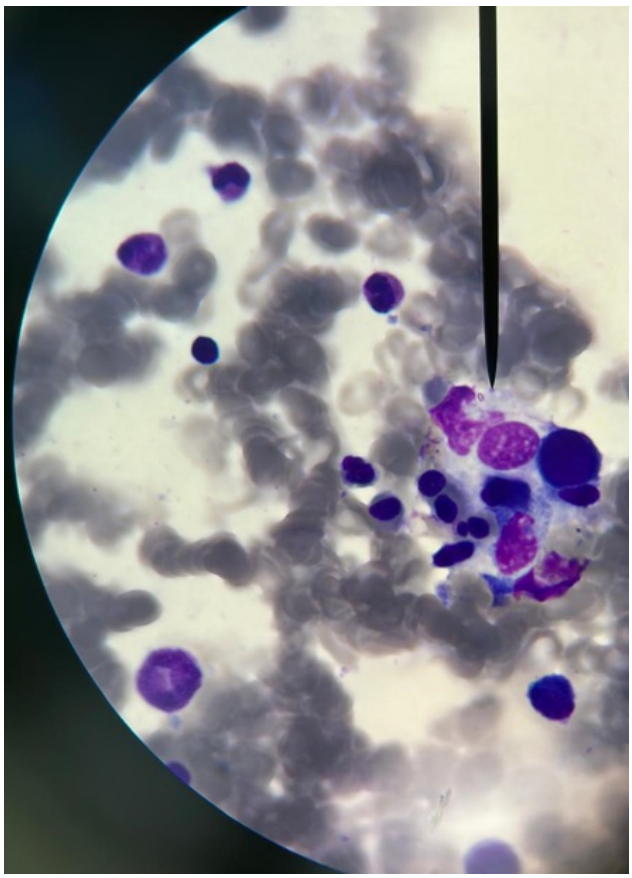


Figure 1. Bone marrow aspirate (Giemsa stain, 100×) showing haemophagocytosis (black arrow) and increased activated macrophages.

demonstrated hypocellular bone marrow, and increased activated macrophages and haemophagocytosis *(Fig. 1)*.

Based on the previous findings meeting the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR)[5] and HLH-2024 criteria[6], the patient was diagnosed with HLH secondary to SLE. She was then admitted to the intensive care unit where she received pulse methylprednisolone (1 g/day intravenous for three days) followed by oral prednisolone (1 mg/kg/day), intravenous immunoglobulin (IVIG; 400 mg/kg/day for five days), hydroxychloroquine (200 mg/day), and empiric meropenem, linezolid, acyclovir and anidulafungin. Filgrastim was administered for cytopenia. Rituximab therapy (two doses of 1 g IV infusion, given two weeks apart) was subsequently added to her treatment regimen after a pre-rituximab workup confirmed no contraindications.

On the third day of treatment with steroids and IVIG, the patient developed psychosis manifested by visual hallucinations and mood swings. To determine whether these manifestations were caused by SLE or steroid therapy, brain MRI was conducted. It revealed non-specific supratentorial white matter hyperintensities *(Fig. 2)*. Therefore, a diagnosis of neuropsychiatric SLE was made. A few days after completing IVIG, the first dose of rituximab and high-dose steroids, hallucinations resolved without antipsychotics. However, subtle mood swings persisted even after stopping steroids. This confirmed neuropsychiatric SLE and excluded steroid-induced psychosis.

Following two weeks of treatment, the patient's condition significantly improved. Her fever subsided, cytopenia was resolved (white blood count 3.2 $\times 10^9$/l, haemoglobin 11.1 g/dl, platelets 210 $\times 10^9$/l), and inflammatory markers declined (ferritin 800 ng/ml, LDH 300 U/l). She was discharged with a plan for close follow-up on hydroxychloroquine, tapering doses of prednisolone (50 mg/day reduced by 5 mg every week until 5 mg/day was maintained) and additional rituximab therapy based on clinical evaluation.

DISCUSSION

We report a rare case of a young female patient presenting initially with secondary HLH due to undiagnosed SLE. Our patient had fever, cytopenia (anaemia and neutropenia), hyperferritinaemia, hypertriglyceridaemia and bone marrow haemophagocytosis, fulfilling five out of the seven HLH-2024 diagnostic criteria[6]. Concurrently, she had positive ANA and anti-dsDNA antibodies, low complement C3 level and systemic inflammatory features meeting the 2019 EULAR/ ACR criteria for SLE[5]. These led to the diagnosis of HLH secondary to SLE. The presentation of HLH as the initial manifestation of previously undiagnosed SLE, as seen in our case, is exceptionally rare as most reported cases in literature describe HLH occurring in patients with established SLE diagnoses.

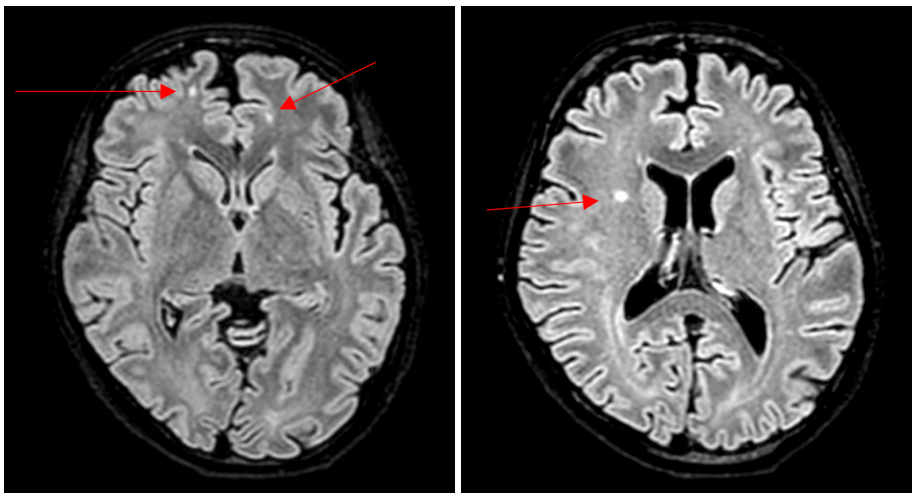


Figure 2. Brain MRI showing non-specific supratentorial white matter hyperintensities.

Our patient initially sought medical care in Georgia with fever and shortness of breath. These symptoms were also reported among her colleagues at that time. This clinical picture raises the possibility of a respiratory infection such as COVID-19, which may have served as the inciting event for HLH and potentially unmasked the underlying SLE. In this context, there was a report that COVID-19 could be a potential trigger for SLE-associated HLH[7].

HLH is difficult to diagnose because of its non-specific clinical and laboratory features. Fever, cytopaenias, hyperferritinaemia and elevated inflammatory markers can sometimes be mistaken for signs of infections or autoimmune diseases, so delayed diagnosis is common[3]. In this case, the patient received multiple courses of antimicrobial therapy in Georgia without improvement before returning to Saudi Arabia. Thus, clinicians should consider HLH early in patients who exhibit persistent fever and systemic inflammation unresponsive to conventional therapies.

Laboratory abnormalities observed in HLH are caused by cytokine dysregulation. Elevated levels of tumour necrosis factor-alpha and interferon-gamma, along with haemophagocytosis, contribute to pancytopenia. Hyperferritinaemia results from increased macrophage activity and heme metabolism, mediated by the cluster of differentiation 163 (CD163) receptor. Hypertriglyceridemia occurs due to cytokine-mediated inhibition of lipoprotein lipase[3].

The treatment approach of secondary HLH is multidisciplinary and includes symptomatic treatment, suppressing inflammation and treatment of the underlying disease. In SLE-associated HLH, high-dose corticosteroids and immunosuppressive agents such as cyclophosphamide and IVIG are usually effective. In our case, the patient showed significant clinical and laboratory improvements after using steroids, hydroxychloroquine, IVIG and rituximab. The latter, a monoclonal antibody that targets B-cell activity, was also administered in a similar case and resulted in a significant improvement[8].

Secondary HLH is a potentially lethal disorder with a high mortality rate – exceeding 60% – if not treated properly, although secondary HLH cases due to autoimmune diseases such as SLE have favourable outcomes[9]. This aligns with our presented case. In contrast, one patient in a case series had a severe disease course and died[10]. This was attributed to presence of multiple poor prognostic factors including thrombocytopaenia (<100 $\times 10^9$/l), leukopenia (<0.4 $\times 10^9$/l) and a triggering bacterial infection. This points out that close follow-up of treatment response is mandatory in such a life-threatening condition.

CONCLUSION

In adult patients with SLE, physicians should consider HLH as a potential initial manifestation. When HLH is suspected to be associated with an underlying connective tissue disease, a comprehensive rheumatological evaluation should be undertaken, even if active infections are present. A targeted therapy such as rituximab or IVIG may be used alongside standard treatment approaches for patients with SLE presenting with HLH. Identifying the underlying cause and initiating immunosuppressive therapy as early as possible are crucial for managing this life-threatening condition.

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