EJCRIM
European Journal
of Case Reports
in Internal Medicine

FEBRILE RASH, SHOCK, AND HYPERFERRITINAEMIA IN A YOUNG WOMAN: NAVIGATING THE DIAGNOSTIC OVERLAP OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS, TOXIC SHOCK, AND VIRAL EXANTHEMA

Pavankumar Hulikere Srinivasaiah[1,2], Kasi Vishwanath Surabhi[3]

[1] Emergency Medicine, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK
[2] Emergency Medicine, Severn PGME School of Emergency Medicine, Bristol, UK
[3] Acute Medicine, Gloucestershire Hospitals NHS Foundation Trust, Gloucester, UK

Corresponding author's e-mail: hspavan8@gmail.com

Received: 08/10/2025
Accepted: 20/10/2025
Published: 04/11/2025

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written informed consent was obtained from the patient for publication of this case report, including all clinical details and images.
Acknowledgments: We thank the multidisciplinary team members involved in the patient's care, including colleagues in dermatology, rheumatology, microbiology, and critical care, for their timely input.
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How to cite this article: Srinivasaiah PH, Surabhi KS. Febrile rash, shock, and hyperferritinaemia in a young woman: navigating the diagnostic overlap of hemophagocytic lymphohistiocytosis, toxic shock, and viral exanthema. *EJCRIM* 2025;**12**:doi:10.12890/2025_005887

ABSTRACT

Background: Fever, rash, and shock in adults pose diagnostic and therapeutic challenges. Markedly elevated ferritin often raises suspicion for hemophagocytic lymphohistiocytosis (HLH), yet hyperferritinaemia is also encountered in sepsis, adult-onset Still's disease (AOSD), and viral infections.

Case report: We describe the case of a 27-year-old woman who developed a high fever, diffuse erythematous rash, hypotension, and markedly elevated ferritin levels. The initial differential diagnoses included toxic shock syndrome, HLH, AOSD, and viral exanthema. Extensive evaluations for infectious, autoimmune, and malignant diseases were negative. Imaging demonstrated gallstones with gallbladder wall inflammation, which was likely the trigger for the systemic inflammatory response. With supportive care and early multidisciplinary input, the patient made a full recovery without the need for immunosuppressive therapy.

Conclusion: This case highlights the importance of contextualising ferritin elevation and maintaining a broad differential diagnosis. Serial laboratory trends, careful use of HLH scoring systems, and multidisciplinary collaboration prevented premature immunosuppression and ensured a favourable outcome.

KEYWORDS

Hyperferritinaemia, hemophagocytic lymphohistiocytosis, toxic shock syndrome, viral exanthem, febrile rash

LEARNING POINTS

- Hyperferritinaemia is a useful biomarker but highly non-specific and must be interpreted within the broader clinical context.
- Serial trends in inflammatory markers and use of scoring tools such as the HScore guide safe decision-making in suspected hemophagocytic lymphohistiocytosis.
- Early multidisciplinary review helps prevent unnecessary immunosuppression and ensures timely supportive care.

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INTRODUCTION

Adults presenting with fever and rash pose a diagnostic challenge, as infectious, autoimmune, and hyperinflammatory disorders often overlap in their early manifestations. Hemophagocytic lymphohistiocytosis (HLH) is an immune dysregulation syndrome characterised by markedly elevated ferritin concentrations, cytopenias, and multi-organ involvement[1,2]. However, hyperferritinaemia is non-specific and is also observed in sepsis, adult-onset Still's disease (AOSD), and viral infections[3,4]. Early differentiation is critical because management diverges significantly: HLH often necessitates immunosuppression, whereas infection- or toxin-mediated syndromes may resolve with source control and supportive measures[5]. We report the case of a young woman whose initial presentation suggested HLH but was ultimately attributed to systemic inflammation triggered by cholecystitis.

CASE DESCRIPTION

A 27-year-old woman, born in the Philippines and raised in the United Kingdom, presented with a 2-day history of intermittent fever, myalgia, and several episodes of non-bilious vomiting. She reported worsening generalised abdominal pain and facial swelling. There was no recent history of travel or known infectious exposures. She worked in a nursing home and was fully vaccinated. Her past medical history included depression treated with sertraline, and recent use of tirzepatide (Mounjaro) for weight loss (>35 kg). She vaped, drank alcohol occasionally, and had no other notable risk factors.

On examination, she was febrile and tachycardic. The abdomen was soft, with minimal tenderness in the right upper quadrant and epigastrium. Over the first 24 hours, she developed a rapidly progressive, diffuse maculopapular rash involving more than 50% of the body surface area, accompanied by erythematous cheeks *(Fig. 1)*, swollen eyelids *(Fig. 2)*, isolated lip swelling without mucosal involvement *(Fig. 3)*, cervical lymphadenopathy, and blanching erythema on the arms and legs.

Initial investigations revealed an elevated C-reactive protein level of 147 mg/l (reference range <5 mg/l). Haemoglobin was 12.9 g/dl (12–15.5 g/dl), white blood cell count 6.5 $\times 10^9$/l (4–11 $\times 10^9$/l), and platelet count 130 $\times 10^9$/l (150–400 $\times 10^9$/l). Liver function tests showed elevated alkaline phosphatase at 231 U/l (30–130 U/l), alanine transaminase at 67 U/l (0–40 U/l), and bilirubin at 41 µmol/l (0–20 µmol/l). A computed tomography scan of the abdomen *(Fig. 4)* demonstrated features suggestive of subacute cholecystitis with associated mesenteric lymphadenopathy.

At approximately 24 hours post-admission, she appeared systemically unwell with a heart rate of 114 bpm, blood pressure 85/60 mmHg, respiratory rate 19 breaths/min, oxygen saturation 98% on 1 l oxygen, and temperature 39°C. She remained alert (Glasgow Coma Scale 15), and her calculated National Early Warning Score was 7, indicating high clinical risk. Despite aggressive fluid resuscitation, her haemodynamic status continued to deteriorate, requiring more than 11 l of intravenous fluids to maintain adequate perfusion and subsequent transfer to the intensive care unit for vasopressor support. Serum ferritin peaked at 2275 µg/l, and her initial HScore was 161, corresponding to an estimated 40–54% probability of HLH. Dermatology review described confluent erythema and conjunctival injection



Figure 1. Facial erythema with cheek and lip swelling.

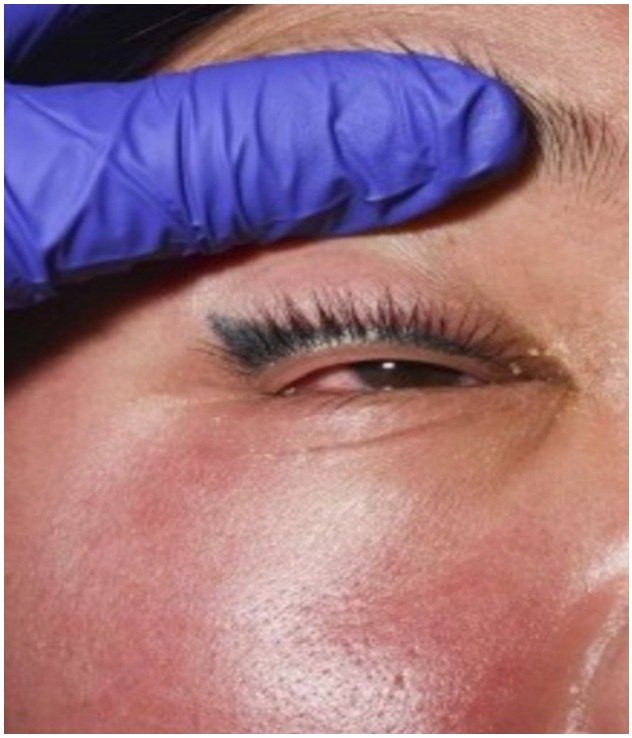


Figure 2. Periorbital erythema and conjunctival injection.

(*Fig. 2*), and a punch biopsy demonstrated a perivascular lymphohistiocytic infiltrate without evidence of malignancy. Rheumatology considered HLH unlikely and favoured AOSD, a toxin-mediated illness, or viral exanthema as alternative diagnoses.

Further investigations included comprehensive virology and serology, which were negative for human immunodeficiency virus, hepatitis B and C, severe acute respiratory syndrome coronavirus 2, Epstein–Barr virus, cytomegalovirus, measles, influenza, parainfluenza, respiratory syncytial virus, adenovirus, and *Bordetella pertussis*. Autoimmune screening, including antinuclear antibody (ANA), double-stranded DNA (dsDNA), antineutrophil cytoplasmic antibody (ANCA), myeloperoxidase (MPO), and proteinase 3 (PR3), was negative. Complement testing showed low C3 with normal C4. Blood cultures were negative apart from a diphtheroid contaminant. Transabdominal ultrasound *(Fig. 5)* demonstrated a thickened gallbladder wall with gallstones, in keeping with acute calculous cholecystitis. Transthoracic echocardiography revealed preserved systolic function without vegetations.

The patient responded well to supportive measures. Vasopressors were discontinued by day 4, coinciding with downward trends in CRP and ferritin. The HScore decreased to 93, corresponding to an estimated ~1% probability of HLH. She continued to improve, was discharged on day 7, and at two-week follow-up reported full recovery with normalised laboratory results. Serial laboratory trends during admission are summarised in *Table 1*.



Figure 3. Isolated lip swelling without mucosal involvement.

DISCUSSION

This case illustrates the diagnostic complexity of febrile rash syndromes with circulatory compromise in young adults. Markedly elevated ferritin concentrations often prompt consideration of HLH[1,2], yet ferritin alone is not diagnostic[3,4]. As an acute-phase reactant, ferritin may rise in sepsis, autoimmune disorders, malignancy, and hepatic injury. Although extreme elevations (>10,000 µg/l) are highly suggestive of HLH, intermediate levels between 1,000 and 3,000 µg/l are frequently observed in critically ill patients[3]. In this patient, the downward ferritin trend with supportive care, together with the absence of additional HLH criteria, argued against HLH as the primary diagnosis.

AOSD is another important HLH mimic, with features including quotidian fevers, rash, lymphadenopathy, hepatitis, and hyperferritinaemia[6]. Macrophage activation syndrome (MAS) complicates up to 15% of AOSD cases[7]. In this case, the rash lacked the evanescent pattern typical of AOSD, and the resolution of inflammatory markers with conservative management rendered AOSD with MAS unlikely.

Toxin-mediated syndromes, such as toxic shock syndrome, may manifest with hypotension, diffuse erythema, and conjunctival injection[5]. Although no definitive bacterial toxin source was identified, empiric antibiotics and source control were appropriately instituted. Concurrently, broad viral polymerase chain reaction testing, and serology were negative, making a viral exanthem less likely. Localised inflammatory processes, such as acute calculous cholecystitis,

	Day 1	Day 2	Day 3	Day 4	Day 6	Reference range
CRP (mg/l)	128 ↑	96 ↑	62 ↑	28 ↑	8 ↑	<5
Hb (g/dl)	12.9	11.8 ↓	12	11.5 ↓	10.7 ↓	12-16
WBC (×10⁹/l)	7.6	10.3	9.5	6.4	9.6	4–11
PLT (×10⁹/l)	130 ↓	131 ↓	134 ↓	147 ↓	298	150–400
Ferritin (µg/l)	2275 ↑	-	1212 ↑	1094 ↑	653 ↑	15–200
Fibrinogen (g/l)	2.39	-	2.09	1.9 ↓	2.19	2–4
Triglycerides (mmol/l)	1.7	2.4 ↑	3.4 ↑	3.1 ↑	3.31 ↑	<1.7
AST (U/l)	47 ↑	38 ↑	62 ↑	83 ↑	-	0–35
H-Score	161	-	-	93	-	-

Abbreviations: CRP, C-reactive protein; Hb, haemoglobin; WBC, white blood cell; PLT, platelet; AST, aspartate aminotransferase.

Table 1. Serial laboratory results during hospital stay. The HScore is a validated tool for diagnosing secondary hemophagocytic lymphohistiocytosis (HLH) in adults. ↑ indicates above the normal reference range, ↓ indicates below the normal reference range.

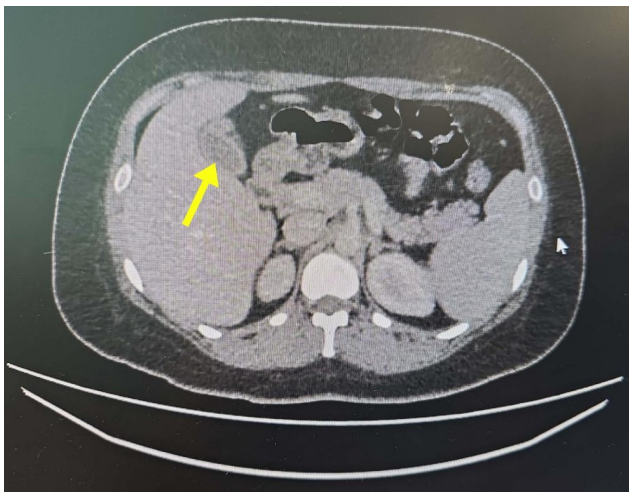


Figure 4. Computed tomography (CT) scan of the abdomen showing mild pericholecystic inflammation. Axial slice from contrast-enhanced CT scan of the abdomen shows pericholecystic fat stranding and mild gallbladder wall oedema (arrow). No intraluminal gallstones are visualized. The findings were indeterminate for cholecystitis and prompted ultrasound correlation.

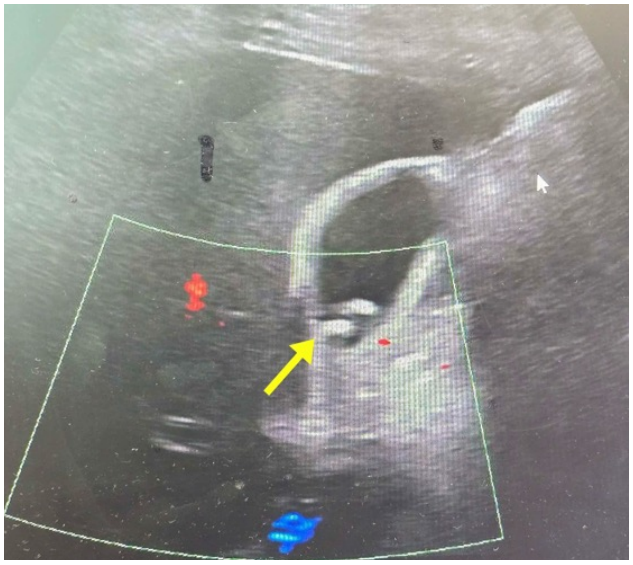


Figure 5. Ultrasound image of gallbladder showing acute cholecystitis. Transabdominal ultrasound demonstrates a thickened gallbladder wall (up to 12.5 mm) with focal oedema and at least two echogenic foci consistent with gallstones (~7 mm) (arrow). No biliary duct dilatation is seen. Findings are in keeping with acute calculous cholecystitis.

can also act as triggers for systemic hyperinflammation, analogous to infection-associated HLH. In this patient, gallbladder inflammation was the most plausible precipitant. Serial biomarker trends, particularly C-reactive protein and ferritin supported a conservative approach without premature immunosuppression. Early multidisciplinary collaboration involving dermatology, rheumatology, clinical microbiology, and critical care was crucial for close monitoring and timely supportive interventions. Although tools such as the HScore can assist in estimating HLH probability, they should not be applied in isolation and must always be interpreted within the clinical context[8]. This case therefore highlights that hyperferritinaemia should be regarded as a warning sign rather than a diagnosis in itself, and that structured interpretation combining biomarkers, scoring systems, and clinical judgement is essential for safe patient care.

CONCLUSIONS

This case highlights the importance of a structured, multidisciplinary approach when evaluating patients who present with fever, rash, shock, and hyperferritinaemia. Although markedly elevated ferritin levels often raise suspicion for HLH, this case illustrates that ferritin is a non-specific marker and must be interpreted in the context of other diagnostic criteria and the patient's clinical course. Over-reliance on ferritin risks premature initiation of immunosuppressive therapy and the potential for unnecessary patient harm.

Clinically, three key implications emerge. First, serial monitoring of inflammatory biomarkers, particularly C-reactive protein and ferritin, provides more meaningful information than isolated measurements and can help guide both the timing and intensity of interventions. Second, maintaining a broad differential diagnosis, including HLH mimics such as AOSD, toxin-mediated illness, viral exanthema, and sepsis, is essential to avoid misdiagnosis and overtreatment. Third, early recognition of reversible, localized inflammatory triggers, as in this case of cholecystitis, is crucial, as appropriate supportive care may be sufficient without the need for immunosuppression.

The broader lesson for clinical practice is that systemic hyperinflammatory presentations demand a careful, stepwise approach. Tools such as the HScore may support risk stratification, but they cannot replace clinical judgment. Early multidisciplinary collaboration between dermatology, rheumatology, clinical microbiology, and critical care specialists ensures coordinated management, minimizes unnecessary interventions, and improves patient safety. By applying these principles, clinicians can enhance diagnostic accuracy, reduce the risk of overtreatment, and optimize outcomes in patients with complex febrile rash syndromes.

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