Case Report

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Unmasking Idiopathic Secondary Hemophagocytic Lymphohistiocytosis in a Young Female: A Diagnostic Challenge Presenting as Pyrexia of Unknown Origin

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Running Title Idiopathic Secondary Hemophagocytic Lymphohistiocytosis with Pyrexia Presentation

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome that can present as prolonged fever of unknown origin (FUO). We describe the case of a 26-year-old woman who presented with two months of intermittent high-grade fever, joint pain, and transient salmon-colored skin rashes. Laboratory investigations revealed cytopenia, elevated triglycerides, abnormal liver enzymes, and a markedly elevated serum ferritin level (>10,000 ng/mL). Extensive evaluation for infectious and autoimmune causes was negative.

Whole-body PET-CT demonstrated diffusely increased marrow activity with small mesenteric lymph nodes, while bone marrow examination confirmed hemophagocytosis. The patient met six of the HLH-2004 diagnostic criteria, and her HScore was calculated at 228, indicating a high probability of HLH. In the absence of any identifiable trigger, a diagnosis of idiopathic secondary HLH was made.

She was treated with dexamethasone monotherapy, which led to rapid resolution of fever, normalization of laboratory parameters, and sustained remission at three-month follow-up. This case underscores the importance of considering HLH early in adults with unexplained fever, cytopenia, and extreme hyperferritinemia, and highlights that corticosteroid monotherapy may be sufficient in selected idiopathic cases.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory disorder caused by uncontrolled activity of cytotoxic T lymphocytes and macrophages, resulting in excessive cytokine release, cytopenia, and multiorgan dysfunction. Although initially described in pediatric patients with inherited defects in immune regulation, adult cases are increasingly recognized in association with infections, malignancies, or autoimmune conditions [1,2]. Diagnosis in adults is particularly challenging because the clinical and biochemical profile—including persistent fever, cytopenia, elevated liver enzymes, hypertriglyceridemia, hyperferritinemia, and splenomegaly—closely mimics sepsis, hematologic malignancies, and systemic autoimmune diseases. Delayed recognition is dangerous, as mortality increases significantly without early treatment [3].

For diagnostic support, two frameworks are frequently applied: the HLH-2004 criteria and the HScore. These integrate clinical, laboratory, and bone marrow findings to estimate the probability of HLH and guide further evaluation. However, neither system is definitive, as false negatives (early or partial presentations) and false positives (critical illness or severe infections) can occur—highlighting the importance of clinical judgment [4,5]. Notably, markedly elevated ferritin levels and rapidly progressive cytopenia should raise suspicion even before all diagnostic elements are met.

Fever of unknown origin (FUO) presents a significant diagnostic challenge, as empirical antibiotic treatments and serial investigations may delay recognition while underlying inflammatory activity persists unchecked [6]. While HLH triggered by infections or malignancy is relatively common, idiopathic secondary HLH—where no underlying cause is identified despite comprehensive testing—is rare and poses unique diagnostic and therapeutic challenges.

We present the case of a young woman with prolonged FUO who met the HLH-2004 diagnostic criteria and had a high HScore, yet no precipitating factor was identified. This report highlights a systematic approach to diagnosis, emphasizes the importance of early bone marrow evaluation, and demonstrates that corticosteroid monotherapy may be sufficient in selected idiopathic adult HLH cases.

Case Presentation

A 26-year-old woman presented to the emergency department with a two-month history of intermittent high-grade fever. Associated symptoms included polyarthralgia affecting the wrists, ankles, and knees, as well as transient, non-pruritic, salmon-colored rashes over the thighs and back. She had previously received empirical antibiotics and antipyretics during hospitalizations at peripheral centers, without sustained improvement.

At presentation, she was conscious and alert but mildly irritable. She was febrile (temperature: 100°F), tachycardic, and clinically dehydrated. General physical examination revealed a coated tongue and mild splenomegaly. Cutaneous examination showed faint, evanescent urticarial rashes over the upper back and posterior thighs. No peripheral lymphadenopathy was noted. Systemic examination of the cardiovascular, respiratory, and central nervous systems was unremarkable.

Given the absence of a clear clinical focus for the fever, a comprehensive infectious disease workup was initiated. All screening tests for common tropical infections—including malaria parasite (MP/MPDA), dengue IgM, typhidot IgM, scrub typhus, and leptospira—were negative. COVID-19 RT-PCR and sputum tests for AFB/Truenat were also negative. Chest radiography and high-resolution CT (HRCT) of the thorax were unremarkable. A non-contrast CT of the abdomen revealed mild splenomegaly, with no hepatomegaly or lymphadenopathy. Serological testing for kala-azar was negative. Both blood and urine cultures remained sterile after 48 hours of incubation.

Baseline hematologic and biochemical parameters are summarized in Table 1.

During febrile episodes, the patient consistently developed faint, erythematous, non-pruritic urticarial lesions over the posterior thighs and upper back. These lesions were transient—resolving within hours—and recurred with each febrile spike. The morphology and timing of the rashes suggested a systemic inflammatory etiology, such as HLH or adult-onset Still's disease (AOSD). The characteristic appearance of the rash is depicted in Figure 1.

In view of persistent fever, rash, hyperferritinemia, and transaminitis, investigations were extended to

Table 1. Key Laboratory and Clinical Parameters at Presentation

Parameter	Observed Value	Reference Range
Hemoglobin	9.6 g/dL	12–16 g/dL
Total Leukocyte Count	19,200/mm³	4,000–11,000/mm³
Neutrophils	78%	40–70%
Lymphocytes	17%	20–45%
Platelet Count	95,000/mm³	150,000–450,000/mm³
Triglycerides	>500 mg/dL	<150 mg/dL
Ferritin	>10,000 ng/mL	13–150 ng/mL (female)
SGOT / SGPT	82 / 96 U/L	<40 U/L
ALP	232 U/L	40–130 U/L
LDH	>1163 U/L	140–280 U/L
CRP	Within normal limits	<5 mg/L

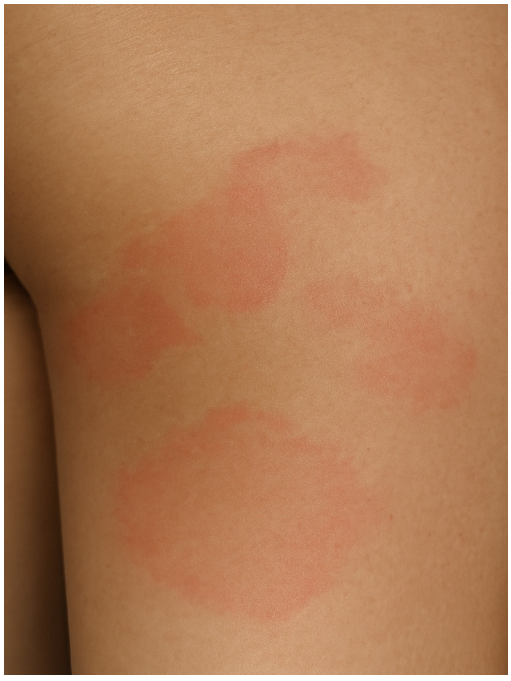

Fig. 1. Clinical photograph of transient, salmon-colored urticarial rash over the posterior thigh during febrile phase.

evaluate autoimmune and neoplastic causes. ANA testing by HEp-2 was positive at a 1:100 dilution, showing nonspecific PCNA and Mi-2 patterns. anti-CCP, rheumatoid factor, ANCA, and antiphospholipid antibodies were all negative. HLA-B27 and serum angiotensin-converting enzyme (ACE) levels were within normal limits. These findings were not suggestive of any defined autoimmune disease.

Given the elevated LDH and systemic signs, malignancy-driven HLH was considered. A PET-CT scan revealed low-grade metabolic activity throughout the bone marrow and a few metabolically active subcentimeter mesenteric lymph nodes. No evidence of overt malignancy, masses, or distant metastasis was found. The imaging findings are illustrated in Figure 2.

To further investigate unexplained cytopenia and systemic inflammation, bone marrow aspiration and biopsy were performed. The marrow was hypercellular, with prominent myeloid hyperplasia. Numerous histiocytes were observed, several demonstrating active phagocytosis of erythroid precursors and other hematopoietic cells. Immunohistochemistry confirmed CD68-positive histiocytes and CD15 positivity among myelomonomacrophages. CD34 was negative, excluding excess blasts. MPO staining highlighted expansion of the myeloid series, while CD20 and CD3 immunostains revealed normal lymphoid populations. A representative smear showing hemophagocytosis is presented in Figure 3.

She fulfilled six of the HLH-2004 diagnostic criteria:

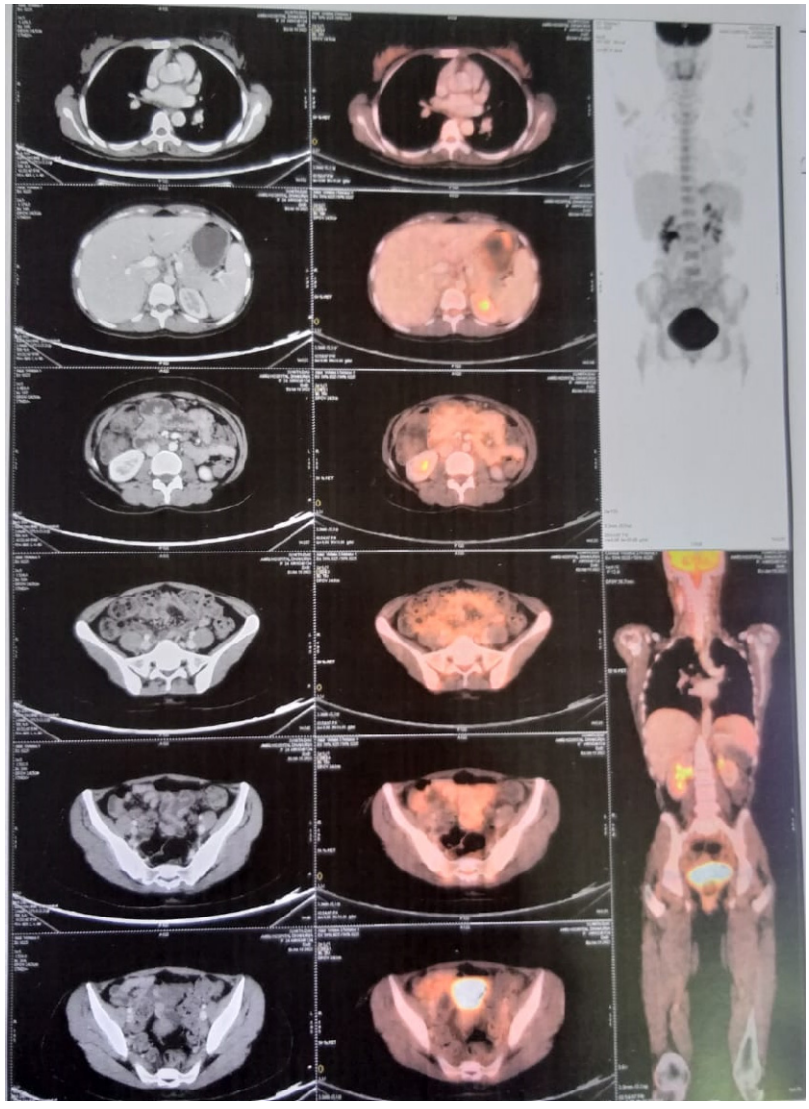

Fig. 2. PET-CT image showing mild splenomegaly and metabolically active mesenteric lymph nodes, suggesting an inflammatory/ reactive process rather than malignancy.

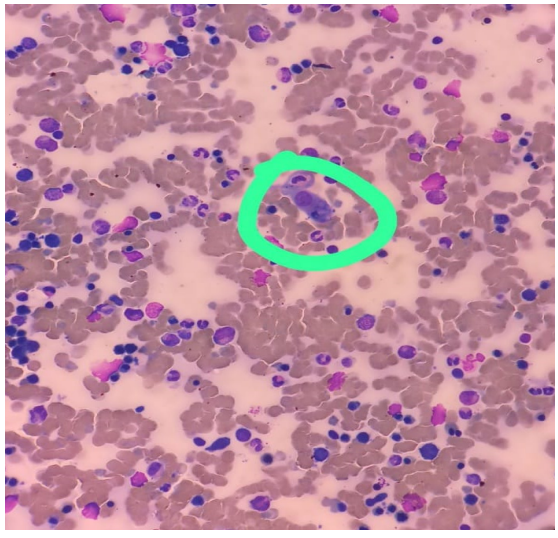

Fig. 3. Bone marrow smear showing a histiocyte engulfing erythroid precursors (evidence of hemophagocytosis).

Table 2. Comparative Analysis of Idiopathic HLH Cases in Adults (2005–2025)

Author(s) & Year	Age/Sex	Diagnostic Criteria Met	Underlying Trigger	Treatment	Outcome
Current study (2025)	26/F	6/8 HLH-2004; HScore 228	None identified	Dexamethasone monotherapy	Full remission
Shah et al., 2023	64/M	6/8 HLH-2004	None identified	Supportive care only	Spontaneous remission
Yadav et al., 2025	45/F	6/8 HLH-2004	Autoimmune markers positive	Methylprednisolone → Prednisolone	Clinical improvement
Reddy et al., 2025	7 adults (mixed)	*Modified HLH criteria*	Mixed (infectious, autoimmune, idiopathic)	Varied (steroids/supportive)	Varied outcomes
Anekar et al., 2025	38/F	5/8 HLH-2004	None identified	Not specified	Poor prognosis

Abbreviations: HLH-2004, pediatric-derived criteria used pragmatically in adults; HScore, adult probability score for reactive hemophagocytic syndrome.

fever >38.5 °C, splenomegaly, cytopenia (hemoglobin <10 g/dL; platelets <100 × 10^9/L), hypertriglyceridemia (>265 mg/dL), ferritin >500 ng/mL, and bone marrow hemophagocytosis. Her HScore was calculated at 228, indicating a high probability of HLH. With infectious, autoimmune, and neoplastic triggers excluded, a diagnosis of idiopathic secondary HLH was established.

Treatment with intravenous dexamethasone, following the HLH-94 protocol, led to clinical improvement within 48–72 hours—marked by defervescence, resolution of rash, and normalization of hematologic and biochemical parameters. She was discharged on day 14 and remains well on a tapering steroid regimen, with no relapse at three-month follow-up.

Discussion

Adult hemophagocytic lymphohistiocytosis (HLH) often hides in plain sight, particularly when presenting as fever of unknown origin (FUO). Its overlap with sepsis, hematologic malignancies, and systemic rheumatic diseases complicates early recognition. Three practical discriminators should raise clinical suspicion: (i) rapidly evolving bi-/pancytopenia, (ii) markedly elevated ferritin, and (iii) hypertriglyceridemia accompanied by liver dysfunction.

In such contexts, applying the HLH-2004 criteria alongside the HScore offers a structured probability estimate; however, neither tool is definitive on its own. Bone marrow hemophagocytosis may be absent in early stages or obscured by reactive changes [7]. Serial laboratory trends, combined with targeted exclusion of infectious, neoplastic, and autoimmune etiologies, remain central to diagnostic decision-making.

In our patient, six HLH-2004 criteria and an HScore of 228 supported a diagnosis of idiopathic secondary HLH, despite the absence of an identifiable trigger. Corticosteroid monotherapy with dexamethasone led to rapid clinical and biochemical improvement, aligning with reports that selected adult, non-malignancy HLH cases may respond to steroid-first strategies when close monitoring and escalation pathways are in place [8].

Nonetheless, adult HLH carries substantial mortality—especially with delayed diagnosis or malignancy-associated disease—making early initiation of immunosuppression critical. Post-remission surveillance is essential to detect relapse or late-emerging triggers. In recurrent cases, selective genetic evaluation for partial cytotoxic pathway defects may be informative.

Comparative reports summarized in Table 2 over the past two decades highlight the heterogeneity in triggers, treatment thresholds, and outcomes. While some idiopathic cases improve with supportive care alone, others require multi-agent therapy. Delayed targeted treatment consistently correlates with worse prognosis.

This variability underscores three key practice points: maintain a low threshold for evaluating HLH in FUO with cytopenia and extreme hyperferritinemia; use HLH-2004 criteria and HScore in tandem; and individualize therapy—starting with corticosteroids in carefully selected idiopathic adult cases, while remaining vigilant for clinical deterioration [9–11].

Conclusion

This case highlights the diagnostic and therapeutic challenges of HLH, particularly idiopathic forms

in adults. Clinicians should maintain a high index of suspicion for HLH in patients presenting with unexplained fever, cytopenia, extreme hyperferritinemia, and systemic features—including characteristic skin manifestations. Early recognition and timely initiation of immunosuppressive therapy remain critical to improving outcomes in this potentially life-threatening syndrome.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

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Conflict of Interests

The authors have no conflict of interest to declare.

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