

Malignancy-Associated Hemophagocytic Lymphohistiocytosis Secondary to Anaplastic T-Cell Lymphoma: A Case Report

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Case Report

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Abstract

Background: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome caused by uncontrolled immune activation. Malignancy-associated HLH (M-HLH), particularly when triggered by T-cell lymphomas, carries an exceptionally poor prognosis and often mimics severe infection, leading to diagnostic delay.

Case Presentation: A previously healthy 25-year-old male presented with high-grade fever, jaundice, and abdominal pain, followed by rapid deterioration with respiratory failure and encephalopathy. Laboratory evaluation revealed pancytopenia, extreme hyperferritinemia, hypertriglyceridemia, hepatic dysfunction, and coagulopathy. Imaging demonstrated extensive lymphadenopathy and massive hepatosplenomegaly. Despite extensive infectious workup, no source was identified. Peripheral smear and initial bone marrow aspiration showed no hemophagocytosis. A second marrow attempt resulted in a dry tap, raising suspicion of underlying marrow pathology. The calculated HScore was 218 (>93% probability for HLH). High-dose corticosteroids were initiated after intubation without clinical response. The patient died on hospital day five. Posthumous bone marrow histopathology confirmed anaplastic large-cell lymphoma (ALCL) of T-cell lineage.

Conclusion: This case highlights how HLH can dominate the clinical picture, obscure the underlying lymphoma, and present without classical features such as hemophagocytosis. A non-diagnostic marrow aspirate or dry tap should prompt further evaluation for malignancy. Early recognition of lymphoma-associated HLH is critical, as delays may lead to rapid and fatal outcomes.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a catastrophic hyperinflammatory syndrome characterized by excessive cytokine release secondary to uncontrolled activation of cytotoxic T lymphocytes and macrophages, leading to rapid multiorgan dysfunction [1, 2]. HLH is traditionally classified into primary (genetic) and secondary (acquired) forms, the latter most commonly occurring in association with infections, autoimmune disorders, or malignancies.

Among malignancy-associated HLH (M-HLH), hematologic neoplasms—particularly T-cell and natural killer (NK)-cell lymphomas—represent the most frequent and lethal triggers [3]. Anaplastic large-cell lymphoma (ALCL) is a mature T-cell lymphoma defined by uniform CD30 expression and, in many younger patients, ALK positivity. ALCL has been repeatedly reported as a precipitant of secondary HLH and is often associated with an aggressive and rapidly fatal course.

HLH associated with T-cell lymphomas frequently mimics severe infection, acute liver failure, or viral illness, leading to diagnostic delays [1, 2, 4]. Importantly, HLH may precede or obscure the diagnosis of the underlying malignancy, further complicating timely management. This case highlights how HLH can dominate the clinical picture, delay recognition of the underlying lymphoma, and progress rapidly despite intensive supportive care.

Case Presentation

A 25-year-old male who smokes 20 pack-years and consumes alcohol occasionally but not heavily, presented to the emergency department on September 17, 2025, with a five-day history of progressively worsening abdominal pain, high fever, and vomiting. The abdominal pain had initially started three months prior but had intensified over the past two weeks, with the peak of discomfort occurring at the time of admission. The pain was localized to the epigastric region and radiated to both hypochondrial areas. It was not associated with food intake and was constant in nature, with no posture providing relief. The pain was described as severe and persistent, with no alleviating factors.

Vomiting occurred following meals, and the patient reported associated anxiety. Additionally, he developed jaundice approximately 10 days prior, initially observed in the eyes and later extending to the hands. Lower extremity edema was also noted, and the patient experienced headaches, cough, and intermittent confusion. Over the last five days, the patient noticed an increase in abdominal girth, and dyspnea progressively worsened. Furthermore, lesions were observed on the patient's tongue, presenting as figures with a white coating on the surface.

On physical examination, the patient appeared critically ill, exhibiting signs of distress. He reported visual disturbances, including blurred vision, and complained of persistent headaches. The patient also experienced dyspnea, which worsened with exertion, but there was no nocturnal dyspnea. A dry cough with white sputum was present.

Pallor was noted in the conjunctiva, and there were visible ecchymoses on both arms. Cardiac and respiratory auscultation revealed normal heart sounds and clear chest auscultation, with no adventitious sounds. Abdominal examination revealed a soft but distended abdomen, with significant hepatomegaly and splenomegaly each palpable approximately 4 cm below the costal margin. Palpation of the abdomen caused tenderness over the entire region. No peripheral lymphadenopathy was detected. The patient was agitated and confused, but showed no signs of meningeal irritation.

Initial laboratory investigations demonstrated severe pancytopenia, markedly elevated ferritin, hypertriglyceridemia, hepatic dysfunction, and coagulopathy (Table 1).

Table 1. Laboratory findings at presentation

Parameter	Result	Reference Range
Haemoglobin (g/dL)	6.3	13–17
White blood cells ($\times 10^9/L$)	2.8	4–10
Platelets ($\times 10^9/L$)	22	150–400
Ferritin (ng/mL)	50,229	30–400
Triglycerides (mg/dL)	210	<150
Fibrinogen (mg/dL)	256	200–400
AST (U/L)	489	<40
ALT (U/L)	193	<40
Total bilirubin (mg/dL)	16	<1.2
Direct bilirubin (mg/dL)	11	<0.3
LDH (U/L)	900	<250
CRP (mg/dL)	25	<0.5
Erythrocyte sedimentation rate (ESR)	65	<20 mm/h
Procalcitonin (ng/mL)	40	<0.5
INR	1.6	0.9–1.1
Albumin (g/dL)	1.9	3.5–5.0

The electrocardiogram was normal. Transthoracic echocardiography showed preserved left ventricular function with an ejection fraction of 70%, indicating preserved left ventricular function, offering no immediate indication of cardiac abnormalities. A contrast-enhanced computed tomography (CT) scan of the chest, abdomen, and pelvis was also conducted. The CT revealed extensive lymphadenopathy involving the mediastinal, perihilar, para-aortic, iliac, and inguinal regions. The liver was markedly enlarged, predominantly involving the left hepatic lobe, without focal lesions or biliary dilatation. The spleen was massively enlarged, measuring 27 cm in its longest dimension, further supporting the clinical suspicion of a systemic process.

At this stage, the combination of persistent high-grade fever, marked hepatosplenomegaly, severe pancytopenia, extreme hyperferritinemia, hypertriglyceridemia, and progressive hepatic dysfunction raised a strong clinical suspicion for hemophagocytic lymphohistiocytosis (HLH). The rapid clinical deterioration with multiorgan involvement further supported the consideration of a hyperinflammatory syndrome. Consequently, a focused diagnostic approach was initiated to evaluate the possibility of HLH while simultaneously investigating potential infectious, malignant, and autoimmune causes.

A targeted viral workup was conducted to rule out infectious causes. Hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV) were all excluded with negative results for HAV IgM, hepatitis B surface antigen (HBsAg), and HCV RNA. Acute cytomegalovirus (CMV) and Epstein–Barr virus (EBV) infections were ruled out by serologic testing. CMV IgM was negative (0.292), and CMV IgG was positive (25.7), while EBV IgM was negative (0.001), and EBV IgG was positive (3.55), indicating past exposure and excluding active infection. Nasopharyngeal swab testing for SARS-CoV-2 returned negative. Leishmaniasis was excluded as a potential diagnosis through PCR testing for Leishmania species, which yielded negative results, given the absence of cutaneous lesions for direct smear evaluation. Malaria was ruled out based on the peripheral blood smear findings, which showed no malarial parasites.

Blood and urine cultures showed no bacterial growth, and sputum culture was negative for tuberculosis. Additionally, a negative antinuclear antibody (ANA) screen excluded autoimmune conditions, while a tuberculin skin test (TST) was negative, ruling out active tuberculosis. Despite broad-spectrum antibiotic therapy, the patient’s clinical condition did not improve.

The peripheral blood smear demonstrated leukopenia with marked toxic granulation in neutrophils and the presence of occasional abnormal blast forms, along with reactive lymphocytes. Red blood cells were reduced in number, normocytic and normochromic, with the presence of some echinocytes. Platelets were decreased in number, appeared enlarged, and showed no true aggregation.

The first bone marrow aspiration was easy to perform and revealed increased granulation with marked hyperactivity of the granulocytic series at all stages of maturation, accompanied by prominent toxic granulation. A notable increase in basophils and eosinophils was observed. There was no increase in blast cells, plasma cells, lymphocytes, or abnormal cellular clusters, and no parasites were seen. Megakaryocytes appeared within normal limits, with mild morphological changes, and nuclear morphology was preserved. Importantly, no evidence of hemophagocytosis was identified.

In the context of persistent high clinical suspicion for hemophagocytic lymphohistiocytosis, a second bone marrow aspiration was attempted but resulted in a dry tap, a finding commonly associated with marrow infiltration or intense inflammatory activity.

Following the peripheral blood smear and bone marrow evaluations, the HScore was calculated to further assess the likelihood of hemophagocytic lymphohistiocytosis. Based on the patient’s clinical presentation and laboratory findings, the calculated score was 218 points, corresponding to a probability greater than 93% for HLH. These results strongly supported the ongoing clinical suspicion despite the absence of hemophagocytosis on the initial bone marrow aspiration [6,7]. (Table 2)

Table 2. Fulfillment of HLH-2004 diagnostic criteria

Parameter	Patient Finding	HLH-2004 Criterion Met	HScore Points
Fever	Persistent high fever $\geq 38.5^{\circ}\text{C}$	Yes	33
Organomegaly	Hepatomegaly and splenomegaly	Yes	38
Cytopenias	Hb 6.3, WBC 2.8, PLT 22 (3 lineages)	Yes	34
Ferritin	50,229 ng/mL (>6000)	Yes	50
Triglycerides	210 mg/dL (≈ 2.37 mmol/L)	Yes	44
Fibrinogen	256 mg/dL (>250 mg/dL)	No	0
AST	489 U/L (≥ 30)	Yes	19
Hemophagocytosis	Not seen initially	No	0
Immunosuppression	None	No	0
NK activity	Not available	N/A	—
sCD25	Not available	N/A	—
Total HScore			218

Posthumous bone marrow histopathological examination revealed diffuse infiltration by atypical lymphoid cells. Immunohistochemical staining demonstrated strong membranous and paranuclear positivity for CD30 with CD3 expression, while CD20 was negative, confirming a CD30-positive T-cell lymphoproliferative disorder consistent with anaplastic large-cell lymphoma (Figure 1).

Figure 1. Bone marrow histopathology and immunohistochemistry

Within 24 hours of admission, the patient's condition deteriorated rapidly with the development of acute hypoxic respiratory failure and worsening altered mental status. He was transferred to the intensive care unit, where endotracheal intubation and mechanical ventilation were required. Following intubation, high-dose intravenous methylprednisolone (1 g daily for three days) was initiated as part of immunosuppressive therapy. Despite treatment, the patient's clinical course was complicated by refractory shock, generalized tonic-clonic seizures, and progressive encephalopathy, ultimately leading to death on the fifth hospital day.(Table 3).

Table 3. Timeline of Clinical Events and Management

Timeline / Date	Clinical Events, Diagnostics & Interventions	Outcomes
~3 months prior	Onset of mild epigastric pain.	Managed conservatively.
~2 weeks prior	Intensification of epigastric pain radiating to both hypochondria.	Progressive discomfort.
~10 days prior	Onset of jaundice (eyes, then hands).	Deterioration.
September 12, 2025 (~5 days prior)	Onset of high fever, postprandial vomiting, lower extremity edema, dyspnea, and oral lesions.	-
September 17, 2025 (Day 1)	Hospital Admission. Severe pancytopenia, marked hyperferritinemia (50,229 ng/mL), CT showing hepatosplenomegaly (spleen 27 cm) and extensive lymphadenopathy. First bone marrow aspirate: hyperactive granulopoiesis, no hemophagocytosis.	Clinical suspicion of HLH raised (HScore = 218).
Day 2	Rapid clinical deterioration, acute hypoxic respiratory failure, encephalopathy. Transfer to ICU, endotracheal intubation.	Second bone marrow aspiration attempted (dry tap). High-dose IV methylprednisolone initiated.
Days 3–4	Refractory shock, generalized tonic–clonic seizures, progressive encephalopathy.	Unresponsive to high-dose steroids and broad-spectrum antibiotics.
Day 5	Cardiac arrest / Death.	Posthumous bone marrow histopathology confirmed Anaplastic Large-Cell Lymphoma (CD30+ T-cell).

Discussion

This case illustrates the fulminant and deceptive presentation of malignancy-associated hemophagocytic lymphohistiocytosis (M-HLH), in which the hyperinflammatory syndrome dominated the clinical picture and obscured the underlying diagnosis of anaplastic large-cell lymphoma (ALCL). The patient initially presented with features suggestive of infection and acute liver dysfunction, a presentation well recognized to delay the recognition of HLH in adults.

HLH is a life-threatening hyperinflammatory syndrome resulting from ineffective immune regulation and uncontrolled activation of macrophages and cytotoxic T cells. In adults, secondary HLH predominates, with malignancy-associated HLH representing the most lethal form. T-cell lymphomas, including ALCL, account for a disproportionate number of cases and are associated with extremely poor outcomes. [1,2,3,5]

The relationship between ALCL and HLH is increasingly recognized. Malignant T cells are capable of producing large quantities of pro-inflammatory cytokines, including interferon- γ , tumor necrosis factor- α , and interleukin-6. This cytokine storm directly activates macrophages and perpetuates the hemophagocytic process, explaining the extremely rapid clinical deterioration observed in such cases. [11] HLH may therefore present as a paraneoplastic syndrome and frequently precede the histologic diagnosis of lymphoma, as occurred in this patient [3].

A critical diagnostic point highlighted by this case is that the absence of hemophagocytosis or activated macrophages on initial bone marrow aspiration does not exclude HLH [6, 9]. Hemophagocytosis is a dynamic and often late histopathologic finding, with limited sensitivity early in the disease course. Notably, this patient fulfilled the clinical picture of HLH despite the absence of hemophagocytosis and without hypofibrinogenemia. This underscores a key limitation of the HLH-2004 diagnostic criteria, which rely on findings that may be absent in the early stages of adult disease, potentially delaying diagnosis in malignancy-associated HLH.

Current guidelines and expert reviews emphasize that bone marrow evaluation should be repeated when clinical suspicion remains high. In this context, a non-diagnostic aspirate or a dry tap should heighten concern for underlying marrow infiltration or intense inflammatory activity and prompt further investigation. [11]

Severe hepatic involvement was prominent in this case, a common feature in adult HLH and a marker of poor prognosis [8,13]. The degree of liver dysfunction limited therapeutic options and precluded the use of etoposide-based regimens recommended in HLH-94 and HLH-2004 protocols. In a study by Vick et al., leukemias and lymphomas accounted for 97% of malignancy-associated hemophagocytic lymphohistiocytosis cases, with T-cell lymphomas representing the most prevalent subtype and accounting for 46% of cases [12]. Despite prompt initiation of high-dose corticosteroids, the hyperinflammatory process remained uncontrolled. This diagnostic delay reflects a well-recognized limitation of current HLH criteria, which rely on features that may be absent early in the disease course.

This case underscores the aggressive nature of lymphoma-associated HLH and the extremely narrow therapeutic window available for intervention. It highlights the need for clinicians to maintain a high index of suspicion for HLH in adults presenting with sepsis-like illness, cytopenias, and organomegaly, even when classical diagnostic criteria are incomplete. Early recognition, repeated bone marrow evaluation, and urgent investigation for underlying T-cell malignancy are crucial, as delays in diagnosis may result in rapid and fatal disease progression despite supportive care.

Conclusion

This case illustrates the fulminant course of malignancy-associated HLH secondary to anaplastic T-cell lymphoma in a young adult [3]. It highlights how HLH can dominate the clinical presentation and obscure the underlying malignancy, even in the absence of hemophagocytosis or classical diagnostic features early in the disease course. Clinicians should maintain a high index of suspicion for HLH in patients

presenting with sepsis-like illness refractory to antimicrobial therapy, particularly when accompanied by cytopenias, hyperferritinemia, and hepatosplenomegaly. A non-diagnostic bone marrow aspirate or a dry tap should prompt further investigation for underlying marrow pathology. Early recognition and urgent evaluation for lymphoma-associated HLH are critical, as delays may lead to rapid and fatal outcomes despite supportive care.

Declarations

Ethics approval and consent to participate

Ethics approval was not required for this case report in accordance with institutional policy. Written informed consent to participate was obtained from the patient's next of kin.

Consent for publication

Written informed consent for publication of this case report and any accompanying images was obtained from the patient's next of kin. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials

All data generated or analyzed during this study are included in this published article. Additional information is available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Rama Tarsha Kurdy, Mahmoud Alhamadeh Alswij, Khaled Kalalib Al Ashabi, Sozan Abohajar, and Omar Nabil Saab contributed to patient management, data collection, literature review, manuscript drafting, and manuscript preparation. Ebtesam Zahra and Mais Musleh supervised the work, provided clinical expertise, and critically reviewed and revised the manuscript for important intellectual content. All authors contributed to the development of the manuscript, read and approved the final version, and agree to be accountable for all aspects of the work.

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Authors' information

Not applicable.

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Figures

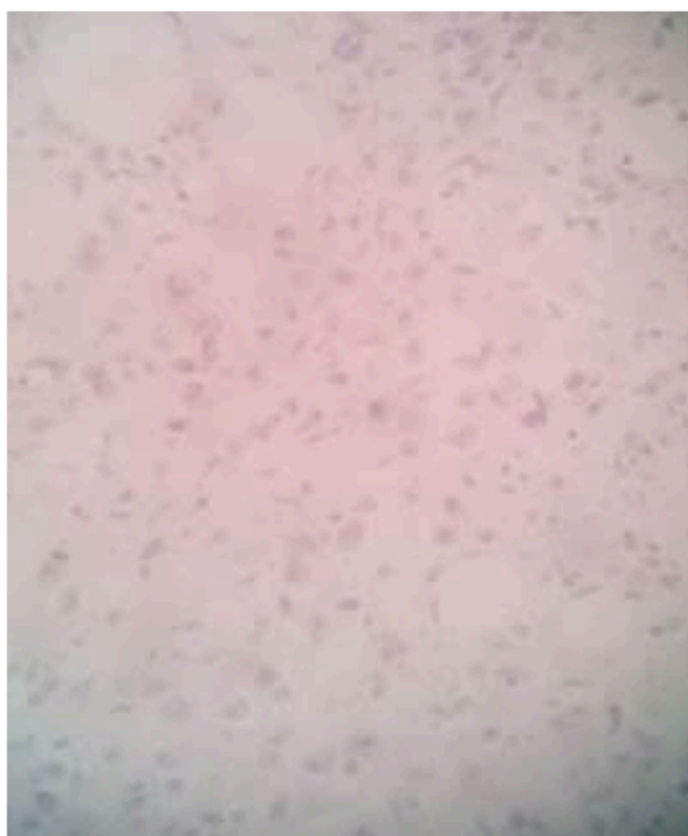
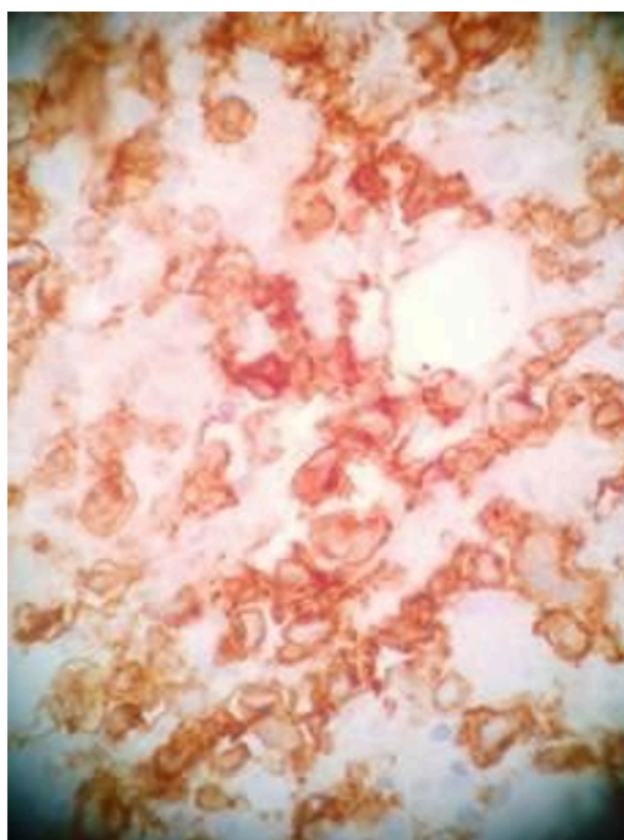
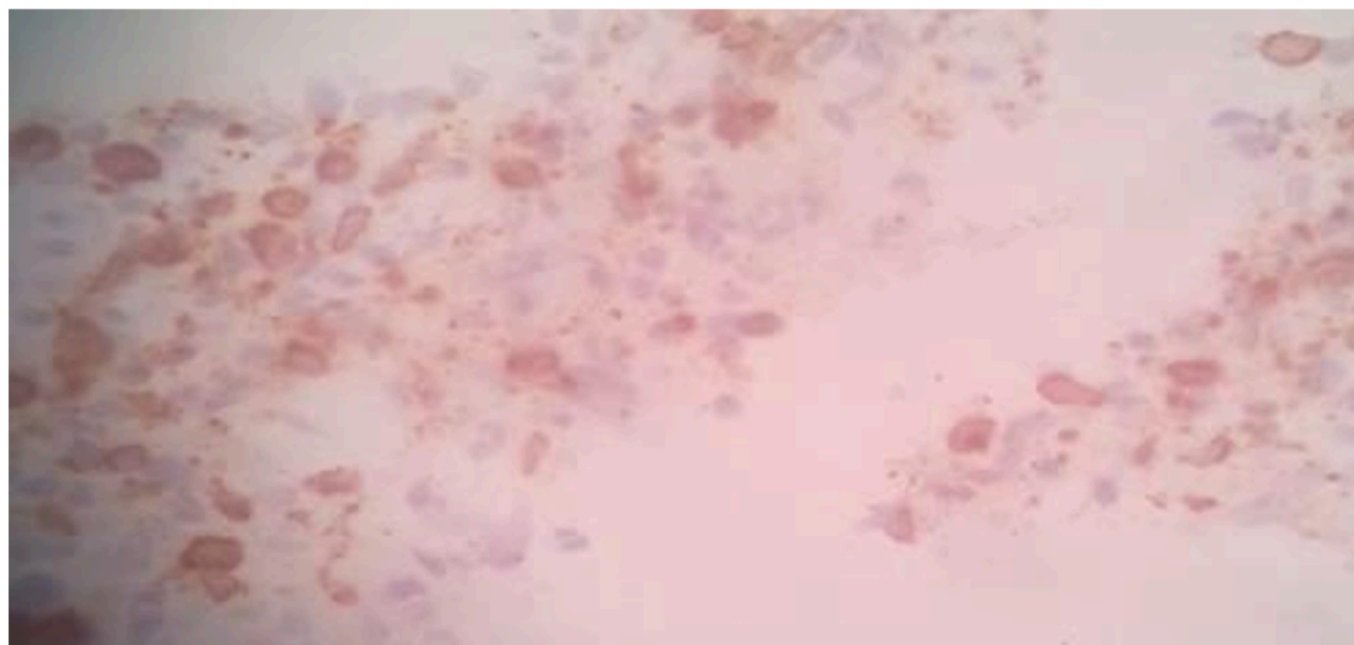


Figure 1

Bone marrow histopathology and immunohistochemistry