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PROGNOSTIC IMPACT OF AETIOLOGY IN ADULT HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: INSIGHTS FROM AN INTENSIVE CARE UNIT EXPERIENCE

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ABSTRACT

Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening hyperinflammatory syndrome marked by excessive immune activation. It can be triggered by various factors, including infections, malignancies, and autoimmune diseases, making the diagnosis challenging due to its overlap with other severe conditions.

Case reports: We discuss two intensive care unit (ICU) cases illustrating the diverse manifestations of HLH and the critical importance of early recognition and treatment. The first case involves natural killer-cell leukaemia, and the second, a suspected viral trigger. Both highlight the necessity of a multidisciplinary approach in diagnosis and management, emphasizing the complexity of HLH in ICU settings.

Conclusions: High mortality rates, particularly in malignancy-associated HLH, underscore the importance of tailored treatment strategies based on the underlying aetiology.

KEYWORDS

Hemophagocytic lymphohistiocytosis, Epstein-Barr virus, NK-leukemia, organizing pneumonia, viral infections

LEARNING POINTS

- Hemophagocytic lymphohistiocytosis (HLH) in adults can arise from a variety of triggers, including infections and malignancies, each influencing disease progression and prognosis differently. Recognizing these underlying aetiologies is crucial for tailoring management strategies and anticipating clinical outcomes.
- Due to its life-threatening nature, HLH requires prompt diagnosis and a coordinated, multidisciplinary approach. Early intervention, incorporating immunosuppressive therapies and supportive care, is essential to improve patient outcomes, particularly in intensive care unit settings where disease severity is often pronounced.
- Utilizing diagnostic tools such as the HScore and HLH-2004 criteria can facilitate early identification of HLH in critically ill patients with unexplained inflammatory symptoms. These tools, along with a high index of suspicion, help distinguish HLH from other hyperinflammatory conditions, enabling timely and appropriate therapeutic interventions.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening syndrome marked by excessive immune activation, driven by activated macrophages and lymphocytes[1]. Described first in 1939[2], HLH represents a hyperinflammatory spectrum caused by genetic factors or triggers like infections, malignancies, and autoimmune diseases[3]. Diagnosing HLH remains challenging due to its varied presentation and overlap with other severe hyperinflammatory conditions, often requiring intensive care unit (ICU) care due to high mortality rates, which range from 41 to 68% in adults[4]. A multidisciplinary approach and early treatment are crucial to improve outcomes, as delays can lead to rapid deterioration.

CASE DESCRIPTION

Case 1: A previously autonomous 74-year-old woman, with a past medical history of hypertension and chronic gastritis, was admitted with a 2-week history of progressively worsening dyspnoea, which had escalated to dyspnoea at rest. She also reported occasional dry cough without haemoptysis and no documented fever, although she had been taking paracetamol and ibuprofen. She had been in contact with family members with upper respiratory infections. A thorough review of her recent medical history, epidemiological context, and potential environmental exposures revealed no significant findings and no apparent immunosuppression was identified. Upon admission to the ICU, the patient remained oriented, but exhibited a low blood pressure profile and severe hypoxemic respiratory failure (P/F ratio <100), requiring high-flow oxygen therapy. Despite the absence of clear respiratory distress, physical examination revealed bilateral velcro-like crackles, more pronounced in the lower lung fields. The remainder of the physical examination revealed no significant findings. Her general condition showed significant respiratory fragility, with desaturation occurring during minimal exertion, such as conversation. A computed tomography (CT) scan revealed scattered bilateral ground-glass opacities, with a consolidative pattern in the right upper lobe and both lower lobes, without pleural effusion *(Fig. 1)*. Extensive microbiological investigation, including respiratory viruses, urinary antigens, blood cultures, mycobacteriological, fungal and *Bordetella pertussis* tests, yielded no significant findings. ICU admission was warranted due to severe respiratory failure requiring non-invasive support with high-flow oxygen. Additional investigation with bronchoscopy showed scant mucous secretions and no macroscopic abnormalities. Bronchoalveolar lavage immunophenotyping indicated lymphocytic alveolitis. Given the findings, a bacterial infection was deemed less likely, though viral or atypical infections could not be excluded, leading to a 5-day course of azithromycin and 2 days of ceftriaxone, which was discontinued due to low suspicion of a typical bacterial cause. Due to the conspicuous imaging findings and the possibility of interstitial disease or organizing pneumonia, corticoid therapy (methylprednisolone 1 mg/kg/day) was also started and resulted in overall clinical improvement, including on inflammatory response and respiratory failure. However, within a week, the patient's respiratory failure worsened again. As such, a lung biopsy was performed and histopathological examination revealed marked fibrin deposition within the alveolar spaces, accompanied by moderate to severe lymphoid inflammatory infiltrates and expansion of the alveolar septa by connective tissue, consistent with acute fibrinous and organizing pneumonia (AFOP). Importantly, there were no histological features suggestive of a lymphoproliferative disorder, nor were there any signs of it on CT scan of the chest abdomen and pelvis. Immune workup found no relevant changes. Upon corticoid weaning, the patient developed fever, accompanied by a modest rise in inflammatory markers and significant thrombocytopenia, later progressing to pancytopenia *(Table 1)*. The patient also exhibited a cholestatic liver enzyme pattern *(Table 1)*, prompting further investigation. Reactivation of Epstein-Barr virus (EBV) was then suspected and serologies and molecular biology assays confirmed it. Given the disproportionate and persistent clinical impact, further studies were ordered to evaluate for HLH, which revealed hypertriglyceridemia, fibrinogen consumption, and hyperferritinemia *(Table 1)*. The patient then met five of the eight HLH-2004 diagnostic criteria, including fever, splenomegaly, pancytopenia, hypertriglyceridemia, and hyperferritinemia. A HScore of 266 points suggested a probability of HLH exceeding 99%. Despite high-dose corticoids, antiviral therapy with rituximab, as well

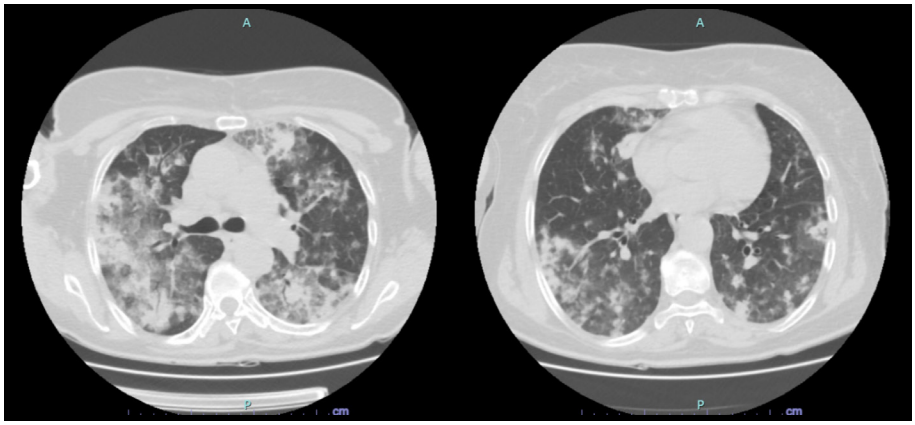


Figure 1. Chest CT scan showing exuberant areas of parenchymal densification, including regions of predominantly ground-glass opacity with a multilobar distribution, assuming a more consolidative appearance in the basal segments of the right upper lobe and in both lower lobes.

Parameters (reference value)	D1	D8	D18	D20	D22	D26	D30
	Corticoids - methylprednisolone 1 mg/kg/day						
					RTX 0.5 g		
					IVIG 0.5 g/kg/day		
						Anakinra 200 mg q8h	
Haemoglobin (12-16 g/dl)	13.3	12.1	11.4	10.4	9.1	7.8	8.3
Leukocytes (4-11 ×10³/µl)	6.37	6.5	4.61	3.39	2.92	1.78	1.69
Platelets (150-400 ×10³/µl)	329	242	67	44	36	43	38
AST (5.0-34.0 U/l)	34	32	72	281	723	456	291
ALT (<55.0 U/l)	28	28	110	369	1170	798	486
GGT (<38 U/l)	22	17	71	196	391	360	336
ALP (40-150 U/l)	72	58	89	234	462	521	513
Bilirubin total/direct (0.2-1.2/<0.5 mg/dl)	0.5	0.4	0.5	0.5	0.9	2.3/1.7	9.7/7.9
Ferritin (15-150 ng/ml)	-	-	-	-	21689.41	64869.81	84904.35
LDH (125-220 U/l)	-	-	-	-	281	297	447
C-reactive protein (<5.0 mg/l)	60.4	15.4	45	53.6	42.1	37.1	105.7
Fibrinogen (2.38-4.98 g/l)	-	-	-	-	1.88	1.81	2.11
Triglycerides (< 150 mg/dl)	-	-	-	-	281		414
EBV PCR			Positive				

Abbreviations: D, day; RTX, rituximab; IVIG, intravenous immunoglobulin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; EBV, Epstein-Barr virus; PCR, polymerase chain reaction.

Table 1. Case 1 - laboratory parameters.

as intravenous immunoglobulins and best supportive care, the patient's condition continued to deteriorate. A trial of anakinra also proved ineffective. Bone marrow aspiration and biopsy revealed not only hemophagocytic lymphohistiocytosis, but immunophenotypic features consistent with natural killer (NK)-cell leukaemia ($CD30^+$), a rare and aggressive malignancy, likely responsible for the patient's clinical course.

The patient became increasingly symptomatic, with fever, marked asthenia, jaundice, and respiratory distress. Despite these challenges, she remained comfortable, with fever being the most distressing symptom. Given the diagnosis of NK-cell leukaemia and its association with hemophagocytic syndrome, and the lack of effective treatment options, the focus shifted to symptom management and comfort care. All immunosuppressive therapy was discontinued. The patient experienced a rapid decline, culminating in multi-organ failure, including worsening hypoxemic respiratory failure and hepatic insufficiency, and ultimately passed away.

Case 2: A 53-year-old woman, with a past medical history of smoking, obesity, and hypertension, was admitted due to respiratory failure associated with fever and pancytopenia of unclear aetiology. The patient initially presented to the emergency department with a 2-day history of fever, reaching 40.5°C, partially responsive to antipyretics. The fever was associated with nasal obstruction, rhinorrhoea,

and frontal headache, without accompanying cough. There were no symptoms of nausea, vomiting, diarrhoea, or skin eruptions. Of epidemiological significance was her exposure to her daughter with a probable viral respiratory infection, colleagues with respiratory symptoms, and a workplace environment contaminated by rats.

She was initially treated empirically with ceftriaxone for 3 days for fever of unknown origin. A CT scan of the chest, abdomen, and pelvis revealed no abnormalities. However, the patient later developed hypotension, worsening pancytopenia, and persistent respiratory failure, leading to her transfer to the ICU. On ICU admission, the patient presented with low-grade fever, tachypnoea, and dyspnoea on minimal exertion, and mild respiratory failure requiring 30% fraction of inspired oxygen (FiO_2). Despite a history of hypertension, the patient's blood pressure remained consistently low with a minimum mean arterial pressure of 50 mmHg, without vasopressor support, and heart rate varied between 90 and 115 bpm, while mild hyperlactatemia persisted, ranging from 2.5 to 3.5 mmol/l. The remainder of the physical examination was largely unremarkable. The patient met five out of eight criteria for HLH according to the 2004 HLH criteria, including fever, cytopenia, hypertriglyceridemia and hypofibrinogenemia, hyperferritinemia, and elevated soluble CD25 *(Table 2)*. Additionally, she had hepatomegaly with significant hepatic cytolysis, which contributed to an individual HScore of 239 points, indicating a 98-99% probability of HLH. An extensive etiological study yielded negative results for infections, malignancies, and autoimmune conditions. Specific tests for viral, bacterial, and parasitic infections were also negative. Bone marrow biopsy and bronchoalveolar lavage did not reveal malignancy or significant infections. Given the context and results, a viral trigger without identification of the specific agent appeared most likely. However, over the next 72 hours, the patient's condition worsened, with marked fatigue, increased dyspnoea at rest, and clear signs of respiratory distress, necessitating an increase in FiO2 to 60% via high-flow oxygen therapy, with the P/F ratio of 120-130. In addition, there was a deterioration in neurological status, characterized by progressive decline in consciousness, lethargy, sparse and confused speech, and inability to recognize family members. The patient developed progressive respiratory failure and CT scan showed new-onset diffuse pulmonary infiltrates *(Fig. 2)*, consistent with an acute inflammatory response resembling acute respiratory distress syndrome (ARDS). She required intubation and mechanical ventilation for approximately 72 hours before being successfully extubated and transitioned to conventional oxygen therapy. The therapeutic approach was multidisciplinary and key treatments included high-dose corticoids (methylprednisolone 1 mg/kg/day), anakinra and intravenous immunoglobulins (IVIG). Doxycycline was initiated empirically due to the possibility of zoonotic infections. The susceptibility to infections due to immunosuppression was carefully addressed, with a negative tuberculosis screening and opportunistic infections' prophylaxis started. The patient's fever resolved, pancytopenia improved, and key laboratory markers such as fibrinogen, triglycerides, ferritin, and soluble CD25 showed positive trends. At discharge, the patient's most recent imaging revaluation had markedly improved *(Fig. 3)*, with significant resolution of infiltrates, she no longer had respiratory insufficiency, and no other complaints were disclosed. At 2-month follow-up, the patient remains asymptomatic under a low-dose of prednisolone, and laboratory results ensure ongoing recovery.

DISCUSSION

HLH in adults often presents as a severe, life-threatening condition with a complex interplay of underlying causes. The aetiology is crucial in determining prognosis and guiding treatment strategies. In an ICU setting, where patients frequently exhibit severe forms of HLH, identifying the primary cause - whether infectious, malignancy-related, or autoimmune - is essential for effective management.

The HLH-2004 criteria for HLH[5] diagnosis can be established either through molecular diagnosis, identifying mutations in specific genes (such as *PRF1*, *UNC13D*, *Munc18-2*, *Rab27a*, *STX11*, *SH2D1A*, and *BIRC4*), or by meeting at least five out of the following eight clinical criteria: fever; splenomegaly; cytopenia - affecting at least two cell lineages, typically with haemoglobin <9 g/dl, platelets <100,000/ml, and neutrophils <1,000/ml; hypertriglyceridemia and/or hypofibrinogenemia; hyperferritinemia; elevated sCD25; haemophagocytosis in bone marrow, spleen, lymph nodes or liver. However, it is important to note that the last is neither necessary nor pathognomonic for HLH diagnosis. The aforementioned HScore is a tool used to estimate the individual risk of HLH, incorporating factors such as known immunosuppression, fever, organomegaly, cytopenia, hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia, aspartate aminotransferase (AST) levels, and evidence of haemophagocytosis in bone marrow aspirates[6]. A recommended cutoff of 169 points offers 93% sensitivity and 86% specificity, providing accurate diagnosis in 90% of patients.

The traditional distinction between primary and secondary HLH is currently outdated - the more accurate terms are HLH disease and HLH syndrome, respectively[7]. HLH disease predominantly affects paediatric patients, and is closely linked to genetic mutations that impair perforin-dependent cytotoxicity. In contrast, HLH syndrome is not a disease per se, but rather a clinical syndrome of hyperinflammation that can be secondary to various triggers[8], such as infections or immunodeficiencies, malignancies and autoimmune diseases. Viral infections are the leading cause, particularly in children, with EBV being the most commonly associated virus. Other viral triggers include cytomegalovirus, parvovirus, herpes simplex virus, varicella-zoster virus, influenza, human immunodeficiency virus (HIV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),

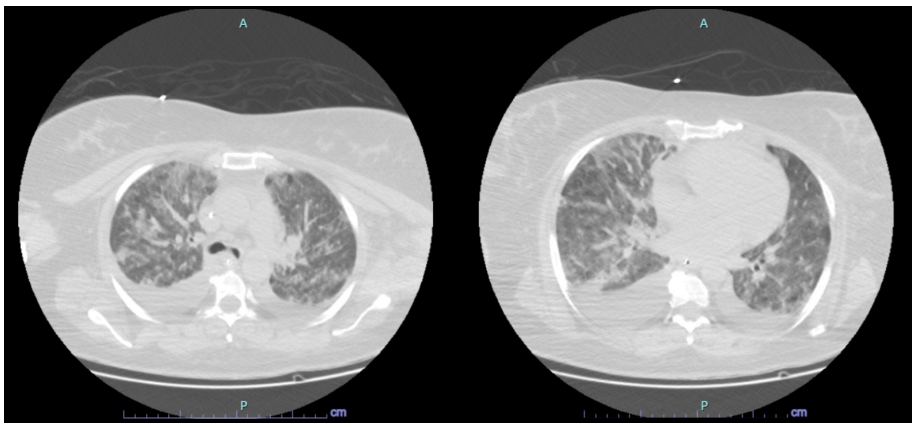


Figure 2. Chest CT showing areas of consolidation in ground glass poorly defined with diffuse distribution in the lung parenchyma, both in the lower and upper lobes and middle lobe, associated with bilateral pleural effusion of moderate volume, probably corresponding to exacerbation of pulmonary oedema.

Parameters (reference value)	**ICU admission**	**D2**	**D3**	**D4**	**D5**	**Discharge**	**2-month follow-up**
	Doxycycline 200 mg/day						
		Corticoids - methylprednisolone 1 mg/kg/day					*Tapering off*
		IVIG 0.5 g/kg/day					
		Anakinra 200 mg q8h					
Haemoglobin (12-16 g/dl)	10.2	10.6	9.6	9.6	9.8	12.5	12.7
Leukocytes (4-11 ×10³/µl)	1.28	1.55	2.1	6.62	8.17	7.91	10.03
Platelets (150-400 ×10³/µl)	36	42	63	57	73	172	212
AST (5-34 U/l)	544	815	502	306	212	39	52
ALT (<55 U/l)	403	618	539	405	302	78	94
GGT (<38 U/l)	271	295	358	492	629	117	102
ALP (40-150 U/l)	66	89	112	143	153	58	53
Bilirubin total/direct (0.2-1.2/<0.5 mg/dl)	1.6/1.3	2.0/1.6	2.2/1.8	1.6/1.1	2.0/1.4	0.5	0.4
Ferritin (15-150 ng/ml)	16476.07	19371.99	12195.23	9344.25	7710.68	457.38	460.7
LDH (125-220 U/l)	656	724	514	517	487	248	264
C-reactive protein (<5.0 mg/l)	10.58	90.5	82.2	40.8	19.9	<1	<1
Fibrinogen (2.38-4.98 g/l)	1.93	1.66	1.32	1.14	1.26	2.76	3.1
Triglycerides (< 150 mg/dl)	-	322	253	-	-	245	156
sCD25 (<2400 U/ml)	9169	-	-	-	1782	-	-

Abbreviations: ICU, intensive care unit; D, day; IVIG, intravenous immunoglobulin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; sCD25, soluble IL-2 receptor.

Table 2. Case 2 - laboratory parameters.

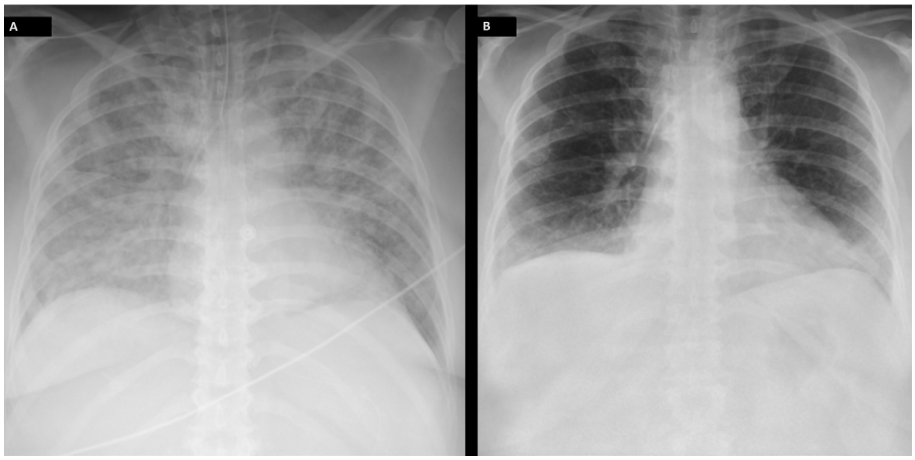


Figure 3. A) Chest X-ray before intubation and mechanical ventilation, with diffuse pulmonary infiltrates, consistent with acute respiratory distress syndrome; B) Radiologic re-evaluation, 12 days later, having finished 10 days of anakinra, 5 days of immunoglobulins and starting corticoid weaning.

while bacterial infections contribute to about 10% of cases, with pathogens like Leishmania, Brucella, and *Mycobacterium tuberculosis* also implicated. In adults, HLH is associated with an underlying malignancy in nearly 50% of cases and may develop as a direct consequence of the malignancy or due to treatments such as chemotherapy, hematopoietic stem cell transplantation, or immunotherapies like chimeric antigen receptor modified T cell (CAR-T) therapy, with lymphomas and leukaemia involved in 20 and 10% of cases, respectively. There is also a strong correlation with systemic juvenile idiopathic arthritis (sJIA) with HLH/macrophage activation syndrome (MAS) in paediatric populations, often co-triggered by infection. Immunodeficiency conditions, including HIV and states of immunosuppression such as post-transplant, chemotherapy, or immunotherapy, can further precipitate HLH[1,3,8].

Regardless, at the heart of HLH is a failure in the regulation of the immune system, often involving defects in the cytotoxic function of NK cells and cytotoxic T lymphocytes (CTL). Normally, these cells target and destroy infected or malignant cells, but in HLH, their function is impaired, leading to uncontrolled activation and proliferation of immune cells. This results in a cytokine storm, a vicious cycle of escalating immune response marked by high levels of interferon-gamma, interleukin-6, and other pro-inflammatory cytokines. The ensuing systemic inflammation can cause multi-organ dysfunction, including hepatosplenomegaly, cytopenia, hyperferritinemia, hypertriglyceridemia, and coagulopathy. Simultaneously, the dysfunctional NK-cells and CTLs lead to macrophagic hyperactivation, triggering phagocytosis of host cells *(Fig. 4)*.

Clinically, HLH presents with a constellation of non-specific symptoms such as prolonged fever, splenomegaly, cytopenia, liver dysfunction, and neurological abnormalities. Coagulopathies, elevated lactate dehydrogenase, ARDS-like pulmonary symptoms, and cardiovascular or renal dysfunction have also been described[8,9].

It is important to note that HLH, multiple organ dysfunction syndrome, and sepsis can coexist, with sepsis potentially acting as a trigger for HLH. The true incidence of HLH syndrome in sepsis remains unknown, possibly underdiagnosed. Distinguishing between HLH and sepsis can be difficult, as HLH may occur in the absence of infection but present with a clinical picture similar to septic shock, acting as a "sepsis mimic"[10]. As aforementioned, HLH can both be triggered by infections and predispose to sepsis due to its underlying immune dysfunction[10]. Ferritin levels above 4,000 µg/l in sepsis significantly increase the likelihood of concomitant HLH, while levels above 10,000 µg/l are highly concerning and may indicate the immediate need for treatment[10].

HLH carries a high acute mortality rate, approximately 40%

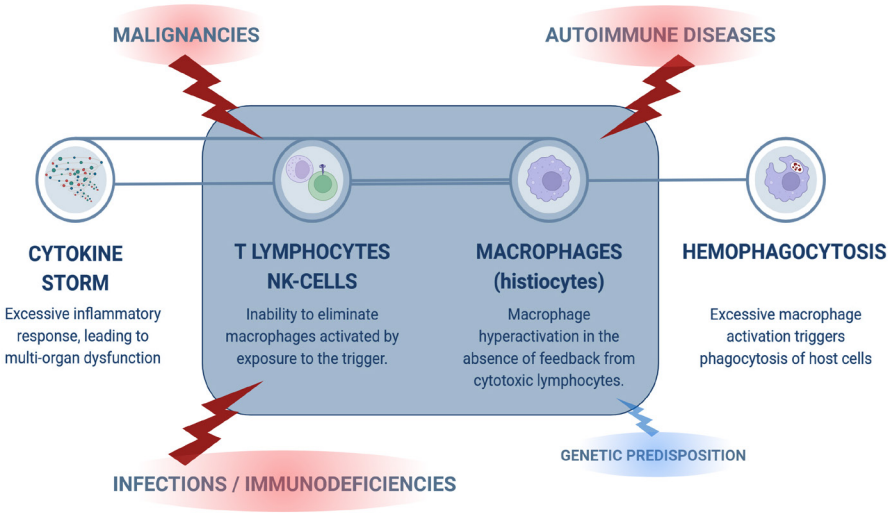


Figure 4. Pathophysiology of HLH.

across all combined groups of aetiologies. HLH associated with malignancy has a particularly poor prognosis, with acute mortality exceeding 80% and a 5-year survival rate of less than 15%. In ICU patients, available evidence describes hospital mortality rates ranging from 52 to 68%[10,11]. The presence of shock or severe thrombocytopenia indicates an increased risk. The peak elevation of serum ferritin is also directly correlated with an increased risk of mortality, whereas a rapid decline in serum ferritin in response to treatment is associated with a more favourable short-term outcome[11].

In these cases, the diverse aetiologies highlight the importance of targeted diagnostic approaches. In Case 1, NK-cell leukaemia was identified as the underlying cause of HLH, emphasizing the critical role of malignancy in the clinical course and prognosis; however the initial findings of EBV infection, were also relevant in the therapeutic strategy, as rituximab has an important role on EBV-associated HLH as antiviral treatment, per updated guidelines[1]. It is also relevant to address the diagnosis of AFOP, as it is a rare and severe form of lung disease characterized by the presence of fibrin in the alveoli and interstitial inflammation, which can complicate the clinical course of patients with underlying conditions such as hematologic malignancies[12]. To the best of our knowledge, this is the first report of AFOP associated with a hematologic malignancy complicated by HLH. The convergence of these conditions underscores their complex and often fatal trajectory, requiring prompt recognition and a coordinated, aggressive therapeutic approach to improve patient outcomes. In Case 2, despite extensive negative tests, a viral trigger was ultimately deemed the most likely aetiology, further supported by the remarkable and rapid response to treatment. This case also highlights the complexity of diagnosing and managing HLH, especially when complicated by severe systemic involvement and respiratory failure. When HLH triggers ARDS[13], the inflammatory cytokine storm associated with HLH exacerbates lung injury, making the condition particularly challenging to manage. Prompt recognition of the interplay between ARDS and HLH is critical, as it necessitates aggressive treatment strategies that address both the underlying hyperinflammation and the resulting respiratory failure.

Active and early screening for HLH in all ICU patients with unexplained hyperinflammation is recommended, along with exhaustive investigation of underlying precipitants (viral infections, immune-mediated conditions, or malignancies) to establish optimal treatment. Understanding the aetiology aids in selecting appropriate treatment regimens and anticipating potential complications. As such, malignancy-related HLH may require specific oncological treatments, while viral or autoimmune-related HLH may benefit from targeted antiviral or immunosuppressive therapies.

This case series underscores the need for comprehensive diagnostic evaluation and tailored therapeutic strategies to improve outcomes in adult patients with HLH syndrome in an ICU setting.

In practice, HLH should be considered in all critically ill patients with unexplained or disproportionate inflammatory responses, including fever, cytopenia, hyperferritinemia, hepatomegaly, splenomegaly, or coagulopathy; particularly those who do not respond to aggressive sepsis treatment. Successful outcomes in HLH cases often rely on prompt recognition, comprehensive diagnostic evaluation and a collaborative approach to treatment, incorporating immunomodulatory therapies.

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