Case Report

Hyperferritinemia and Beyond: Biochemical Insights from a Case Series of Secondary Hemophagocytic lymphohistiocytosis (HLH)

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Keywords

Hemophagocytic Lymphohistiocytosis, Systemic Lupus Erythematosus, Autoimmune Hemolytic Anemia, Severe Dengue, Autoimmune Disease, fever, hyperferritinemia

Abstract

Hemophagocytic Lymphohistiocytosis (HLH) is a rare, life-threatening hyperinflammatory syndrome characterized by excessive immune activation, classified as either primary (familial) or secondary, triggered by infections, malignancies, autoimmune diseases or immune deficiencies. Manifestations include persistent fever, hepatosplenomegaly, cytopenias and elevated ferritin levels. Biochemical markers play a critical role in diagnosing HLH with elevated ferritin, hypofibrinogenemia and hypertriglyceridemia. Three adolescent female cases of secondary HLH highlight the laboratory's critical role in diagnosis and management. In the first (Pseudomonas infection), elevated ferritin, liver enzymes, and low fibrinogen guided antibiotic, steroid, and etoposide therapy. The second, with systemic lupus erythematosus (SLE) and autoimmune hemolytic anemia (AIHA), was diagnosed using elevated ferritin, liver enzymes, and autoimmune markers, managed with hydroxychloroquine and steroids. The third (severe dengue) showed hyperferritinemia, elevated liver enzymes, and hypofibrinogenemia, guiding steroid, iron, and transfusion therapy. These cases highlight the role of biochemical markers in early diagnosis of HLH.

Introduction

Secondary Hemophagocytic Lymphohistiocytosis (HLH) is a critical hyperinflammatory condition that occurs in response to infections, autoimmune disorders, or malignancies [1]. In contrast to the genetic basis of primary HLH, secondary HLH arises due to excessive immune activation from external factors, leading to a cytokine storm and subsequent multi-organ involvement. Patients typically present with persistent fever, hepatosplenomegaly, and cytopenias, often mimicking sepsis or other inflammatory diseases, which makes early recognition difficult. Laboratory parameters, including raised ferritin and liver enzymes, hypertriglyceridemia, and low fibrinogen levels, play a pivotal role in diagnosis [2,3]. This case series discusses three adolescent female patients who developed secondary HLH due to different underlying causes, including systemic autoimmune disease, bacterial infection, and severe dengue infection. These cases emphasize the need to correlate clinical features with laboratory findings for prompt diagnosis and management of HLH, which is vital for improving patient outcomes.

Case series

Case 1

A 16-year-old female presented with a three-month history of fever (102°F), generalized weakness for ten days, itching for two days, and vomiting for two days. She reported migratory joint pains affecting large joints but denied evening fevers, weight loss, or urinary symptoms. On examination, she was pale with multiple enlarged lymph nodes, was fully oriented, and had no neurological deficits. Her abdomen was soft and non-tender with clear breath sounds. Laboratory evaluation revealed anemia, leukocytosis, raised inflammatory markers, and a mild pleural effusion (Table 1). Blood cultures grew Pseudomonas aeruginosa, prompting initiation of Piperacillin-Tazobactam, later escalated to Meropenem due to persistent fever and subsequent leukopenia. Bone marrow biopsy (Figure 1a and Figure 1b) demonstrated hemophagocytosis, while lymph node biopsy showed reactive hyperplasia. Imaging confirmed hepatosplenomegaly and pleural effusion. Elevated ferritin and LDH levels supported the diagnosis of secondary Hemophagocytic Lymphohistiocytosis (HLH). Tropical infections including malaria and dengue were excluded based on clinical assessment, negative serology, and the absence of typical features such as thrombocytopenia or marked liver dysfunction. The diagnosis of secondary HLH was established according to the HLH-2004 criteria based on persistent fever, splenomegaly, cytopenias involving two cell lineages, hypofibrinogenemia, hyperferritinemia, and bone marrow evidence of hemophagocytosis. Management included Meropenem for infection control and dexamethasone for HLH treatment. The patient was advised to monitor her temperature every 4 hours and was prescribed paracetamol 650 mg (maximum four tablets per day), pantoprazole 40 mg once daily before breakfast, calcium once daily, and dexamethasone 6 mg in the morning and 4 mg in the evening, with tapering planned on an outpatient basis.

Figure 1a and Figure 1b: demonstrated hemophagocytosis, while lymph node biopsy showed reactive hyperplasia.

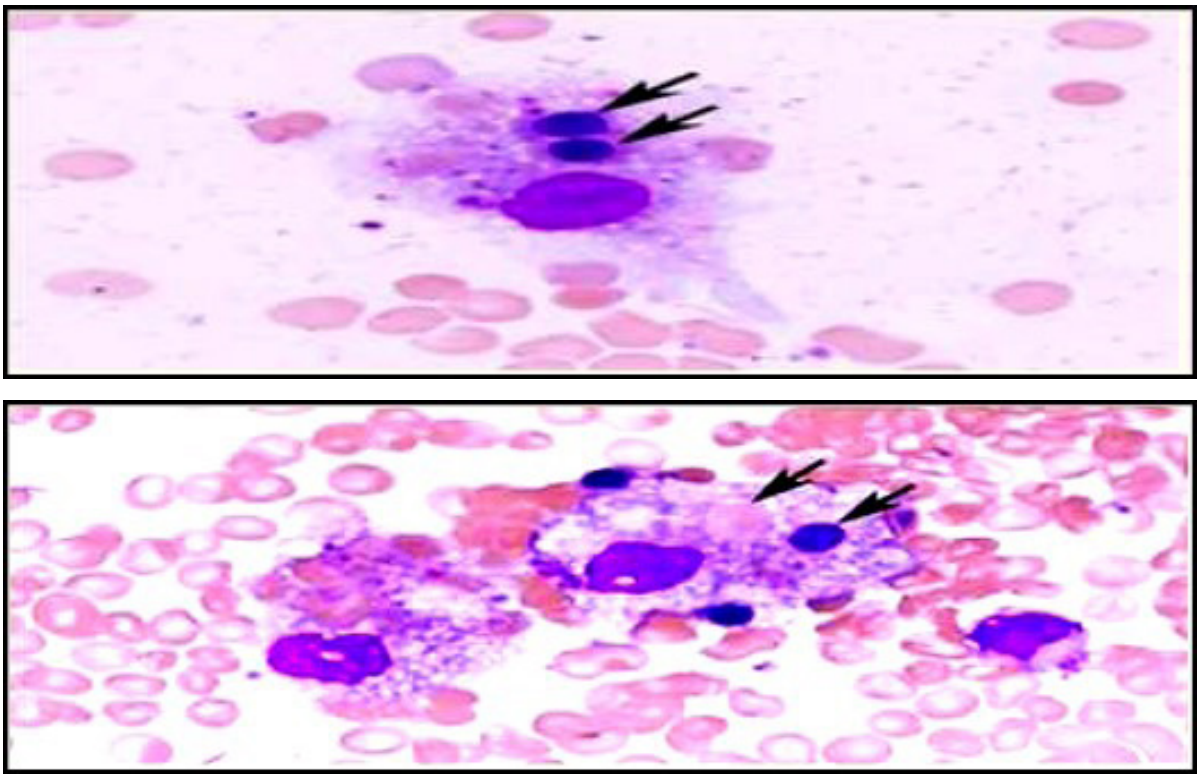


Table 1: Laboratory parameters, imaging, and autoimmune profiles assessed in patients with secondary hlh, aiding diagnosis and monitoring. Values reflect baseline findings prior to initiation of hlh-specific therapy.

Lab Parameter	Normal Range	Case 1	Case 2	Case 3	Machine/Company (Origin)
Hemoglobin (g/L)	120-160	70	76	99	Sysmex XN 1000 (Sysmex Corporation, Japan)
Leukocyte Count (/µL)	4,000-11,000	22,000	9,800	9,900	Sysmex XN 1000 (Sysmex Corporation, Japan)
Platelet Count (× 10^3/µL)	150-450	50	60	120	Sysmex XN 1000 (Sysmex Corporation, Japan)
C-Reactive Protein (mg/L)	<10	212	132	72	Beckman Coulter AU680 (Beckman Coulter, USA)
Ferritin (µg/L)	10-291	>1000	>1500	26,868	Siemens ADVIA Centaur XP (Siemens Healthineers, Germany) & Vitros 5600 (Ortho Clinical Diagnostics, USA)
Fibrinogen (mg/dL)	200-400	50	80	49	Siemens ADVIA Centaur XP (Siemens Healthineers, Germany)
Lactate Dehydrogenase (LDH, U/L)	100-250	1300	600	1512	Beckman Coulter AU680 (Beckman Coulter, USA)
Urinary Microalbumin Creatinine Ratio (µg/mg)	<30	657.44	300	500	Beckman Coulter AU680 (Beckman Coulter, USA)
Direct Coombs Test (DCT)	Negative	Positive	Positive (4+)	Positive (4+)	Bio-Rad
Blood Culture	Negative	Pseudomonas aeruginosa	Negative	Negative	BD BACTEC FX (Becton Dickinson, USA)
Differential Leukocyte Count (%)	A 40-80, L: 20-40, M 2-10, E: 1-6, B: 0-1	N 66.9, L 29.7, M 2.9, E 0.4, B 0.1	N 66.9, L 28.2, M 3.8, E 0.9, B 0.2	N 77.5, L 18.1, M 3.1, E 1.0, B 0.3	Sysmex XN 1000 (Sysmex Corporation, Japan)
Absolute WBC Differentials count (/µL)	–	N: 14,718, L: 6,534, M: 638, E: 88, B: 22	N: 6,556, L: 2,764, M: 372, E: 88, B: 20	N: 7,673, L: 1,792, M: 307, E: 99, B: 30	Calculated by formula
Total Bilirubin (µmol/L)	<20.52	11.2	37.6	117.9	Beckman Coulter AU680 (Beckman Coulter, USA)
Direct Bilirubin (µmol/L)	<5.13	3.42	20.52	99.18	Beckman Coulter AU680 (Beckman Coulter, USA)
ALT (U/L)	10-40	–	111	562	Beckman Coulter AU680 (Beckman Coulter, USA)
AST (U/L)	10-40	–	273	1512	Beckman Coulter AU680 (Beckman Coulter, USA)
Triglycerides (mmol/L)	<1.69	–	5.6	3.3	Beckman Coulter AU680 (Beckman Coulter, USA)
Procalcitonin (µg/L)	<0.5	–	3.0	2.2	Siemens ADVIA Centaur XP (Siemens Healthineers, Germany)
PT (seconds)/INR	9.9-13.0 / 0.8-1.2	–	–	31.6/2.53	Stago STA Compact Max (Stago, France)
Ultrasound abdomen & Chest X-ray Findings	–	Mild pleural effusion	Bilateral mild pleural effusion & splenomegaly	Gross ascites & bilateral mild pleural effusion	Siemens Ysio Max (Siemens Healthineers, Germany)
CECT Scan Findings	–	Hepatosplenomegaly, bilateral pleural effusion	–	–	GE Revolution CT (GE Healthcare, USA)
ANA Pattern	Negative	–	Homogeneous (4+)	–	IIFT (EUROIMMUN, Germany)

PT: Prothrombin time, INR: International normalised ratio, CECT; Contrast enhanced Computed tomography, ANA: anti-nuclear antibodies, IIFT: Indirect immunofluorescence test, ALT: alanine aminotransferase, AST: Aspartate transaminase, LDH: Lactate Dehydrogenase.
Ferritin concentrations in Cases 1 and 2 exceeded the analytical measuring range of the assay and were therefore reported as >1000 ng/mL and >1500 ng/mL, respectively. These values represent the lower limit above the assay's measurable range and should not be interpreted as the actual serum ferritin concentrations.

Case 2

An 18-year-old female presented with a two-month history of intermittent fever, oral ulcers, and joint pain. The fever, accompanied by chills, responded to intravenous paracetamol. Oral ulcers, initially located on the hard palate, progressed to the ventral tongue, causing difficulty in swallowing. Joint pains started in the proximal interphalangeal joints and later affected the ankles and knees. Her history included abnormal body movements eight years prior and oral ulcers three years ago. On examination, she was conscious and oriented but had hypotension (96/52 mmHg) and a high-grade fever (105°F). Respiratory examination revealed bilateral wheezing, and splenomegaly was noted on abdominal examination. Initial laboratory investigations showed anemia, leukopenia, thrombocytopenia, raised C-reactive protein (CRP), and abnormal liver function tests (Table 1). Autoimmune evaluation confirmed systemic lupus erythematosus (SLE) with a positive ANA and positivity for SmD1: 3+, dsDNA, Histone, SSA/Ro-60, CENP-B: 1+, and equivocal results for AMA M2 and Nucleosome antibodies. A strongly positive Direct Coombs

Test (4+) indicated autoimmune hemolytic anemia (AIHA). A diagnosis of SLE complicated by secondary Hemophagocytic Lymphohistiocytosis (HLH) and AIHA was made. The diagnosis of secondary HLH was established according to the HLH-2004 criteria based on persistent fever, splenomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, and hyperferritinemia, fulfilling six of the eight diagnostic criteria. Tropical infections were excluded with negative malaria and dengue serology and absence of other markers. She was started on hydroxychloroquine and prednisolone (40 mg), followed by pulse methylprednisolone therapy due to ongoing anemia and fever. The patient's condition improved with treatment, and a renal biopsy was planned on an outpatient basis to evaluate for lupus nephritis.

Case 3

An 18-year-old female presented with a seven-day history of fever, jaundice, abdominal pain, vomiting, and loose stools. The fever had an abrupt onset, reaching 104°F, and the abdominal pain was localized to the right upper quadrant. On examination, she was icteric, had bilateral pedal edema, and exhibited tenderness in the right upper abdomen. Initial laboratory findings revealed anemia, leukocytosis, and thrombocytopenia. Dengue infection was confirmed by positive IgM and NS1 antigen tests, while screening for other tropical infections (scrub typhus, leptospirosis, malaria, typhoid, hepatitis A and E) was negative. Despite receiving intravenous fluids, antibiotics (ceftriaxone and doxycycline), and antimalarial therapy (artesunate), the fever persisted. Elevated ferritin and triglycerides with low fibrinogen levels supported the diagnosis of secondary Hemophagocytic Lymphohistiocytosis (HLH) (Table 1). The diagnosis of secondary HLH was established according to the HLH-2004 criteria based on persistent fever, cytopenias, hypertriglyceridemia, hypofibrinogenemia, and hyperferritinemia, fulfilling five of the eight diagnostic criteria. Secondary HLH is commonly triggered by severe infections like dengue, resulting in hyperinflammation and multi-organ involvement. The patient was started on dexamethasone, and her condition stabilized with the addition of blood transfusions and iron supplementation to manage anemia. After 10 days of hospitalization, she showed clinical improvement and was discharged with follow-up plans. At discharge, she was advised to maintain adequate oral hydration, monitor blood glucose levels at home, and continue dexamethasone 4 mg twice daily for two weeks, followed by 2 mg twice daily for two weeks, and then 2 mg once daily for one week. She was also prescribed pantoprazole 40 mg once daily before meals for six weeks, paracetamol 650 mg as needed for fever, calcium 500 mg once daily for six weeks, cefixime 200 mg once daily for two days, ursodeoxycholic acid 300 mg twice daily, and rifaximin 550 mg twice daily.

Materials and methodology

This case series included three adolescent female patients diagnosed with secondary Hemophagocytic Lymphohistiocytosis (HLH) at a tertiary care hospital. Clinical history, examination findings, and laboratory investigations were recorded, and the diagnosis of secondary HLH was established according to the HLH-2004 diagnostic criteria. Bone marrow examination was performed when clinically indicated. Hemoglobin, leukocyte count, platelet count, and differential counts were analyzed using Sysmex XN 1000 (Sysmex Corporation, Japan). Absolute differential leukocyte counts were calculated by multiplying the total leukocyte count by the percentage of each cell type divided by 100. C-Reactive Protein (CRP), liver enzymes (AST, ALT), bilirubin, LDH, triglycerides, and urinary microalbumin-creatinine ratio were measured using AU680 analyzer (Beckman Coulter, USA). Ferritin, fibrinogen, and procalcitonin were assessed using ADVIA Centaur XP (Siemens Healthineers, Germany) and Vitros 5600 (Ortho Clinical Diagnostics, USA). Blood cultures were performed using BD BACTEC FX (Becton Dickinson, USA), and the Direct Coombs Test (DCT) was done using Bio-Rad kits (Bio-Rad Laboratories, USA). The Direct Coombs Test (DCT) was performed using Bio-Rad ID-Card (Bio-Rad Laboratories, USA), which detects both IgG and C3d on red blood cells. Coagulation parameters including PT/INR were measured using STA Compact Max (Diagnostica Stago, France). Ultrasound of the abdomen and chest X-ray were performed using Ysio Max (Siemens Healthineers, Germany), while CECT scans were done with Revolution CT (GE Healthcare, USA). Autoimmune profiling, including ANA patterns, was performed using Indirect Immunofluorescence Test (IIFT) on EUROIMMUN kits (EUROIMMUN, Germany).

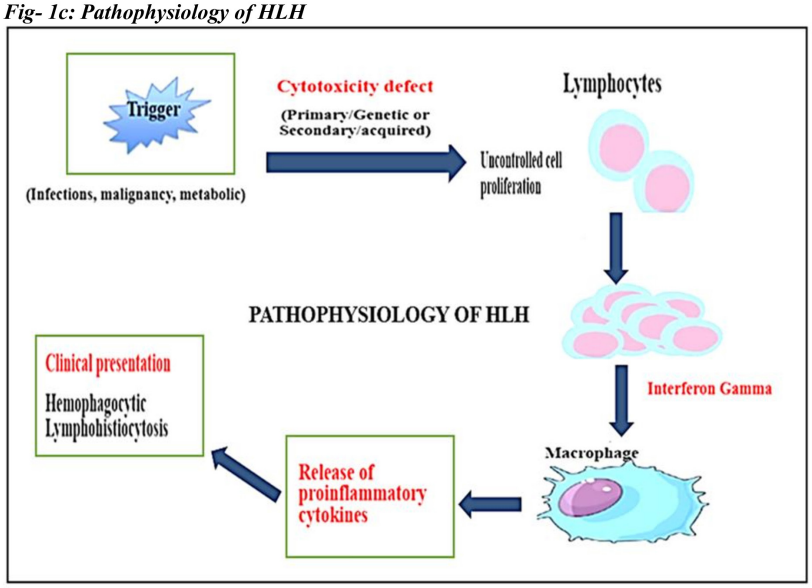
Discussion

In recent years, several innovative strategies have been developed to evaluate patients exhibiting clinical and laboratory findings suggestive of Hemophagocytic Lymphohistiocytosis (HLH). HLH is a severe hyperinflammatory condition with the potential to rapidly advance to multiple organ failure (MOF) and can be fatal [1,2]. It is categorized into primary (familial), arising from genetic defects in the perforin signaling pathway, and secondary (acquired), which occurs in the context of infections, malignancies, or autoimmune diseases [3,4]. When HLH is associated with autoimmune disorders, it is termed macrophage activation syndrome (MAS). The defining feature of HLH is unregulated immune activation involving excessive stimulation of antigen-presenting cells (macrophages and histiocytes) along with CD8+ T cells. This leads to persistent hypercytokinemia, a key driver in HLH pathogenesis, contributing to tissue injury and MOF [5]. Elevated pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-6, IL-12, and IL-18 further amplify the immune response, leading to systemic inflammation (Figure 1c). Diagnosing HLH remains complex due to its non-specific clinical manifestations. The International Histiocyte Society has proposed diagnostic criteria (Table 3) requiring at

least five out of eight specified clinical and laboratory parameters, including fever, splenomegaly, cytopenias, hypertriglyceridemia or hypofibrinogenemia, elevated ferritin, raised soluble IL-2 receptor (sCD25), decreased Natural Killer (NK) cell activity, and the presence of hemophagocytosis. In secondary HLH, infections, particularly viral infections like Epstein-Barr virus (EBV), are the most common precipitating factors. Additional causes of HLH include autoimmune conditions such as systemic lupus erythematosus (SLE), juvenile idiopathic arthritis, vasculitis, and certain cancers like lymphoma and leukaemia. In HLH, excessive immune activation stems from the inability of cytotoxic CD8+ T cells and natural killer (NK) cells to clear target cells effectively, resulting in sustained immune activation and macrophage stimulation. The presence of hemophagocytosis along with elevated cytokines, particularly interferon-gamma (IFN-γ), leads to increased ferritin and TNF-α levels, contributing to key HLH manifestations such as hyperferritinemia, hypertriglyceridemia, and hepatosplenomegaly [6-9]. Recent advances in the understanding of HLH pathobiology have demonstrated that persistent activation of cytotoxic T lymphocytes and macrophages results in uncontrolled cytokine release, leading to immune-mediated tissue injury and multiorgan dysfunction. Improved understanding of these immunological pathways has facilitated the development of targeted therapeutic strategies directed against specific inflammatory mediators [13,15]. According to Ohga S et al., virus-associated hemophagocytic syndrome (VAHS), a subtype of secondary HLH, is characterized by high circulating levels of pro-inflammatory cytokines, especially IFN-γ and TNF-α during active disease, with IFN-γ serving as a critical marker of disease activity and a potent macrophage activator during hypercytokinemia [7]. Patrick DA et al. reported that secondary HLH is associated with elevated pro-inflammatory cytokines including IL-6 and IL-8, driving the hyperinflammatory state that can result in multiple organ failure (MOF), similar to what is observed in trauma patients. They also noted that a delayed increase in soluble Intercellular Adhesion Molecule-1 (sICAM-1) may indicate endothelial injury or inflammation, which is commonly seen as secondary HLH progresses [8]. Henter JI et al. described the HLH-2004 diagnostic criteria, which require fulfilling five out of eight parameters, including the recently added markers of hyperferritinemia, elevated soluble IL-2 receptor levels, and decreased or absent NK-cell activity, thereby improving diagnostic accuracy for secondary HLH (Table 2) [9]. These diagnostic markers are crucial for recognizing secondary HLH triggered by infections, autoimmune conditions, and malignancies. Although the HLH-2004 diagnostic criteria remain the cornerstone for diagnosing HLH, recent recommendations emphasise that these criteria should be interpreted alongside clinical judgement because several laboratory abnormalities may evolve during the course of illness. The North American Consortium for Histiocytosis (NACHO) recommends integrating serial laboratory investigations with clinical assessment to facilitate early diagnosis and timely initiation of treatment, particularly in critically ill patients [14].

Figure 1c: Pathophysiology of HLH.

Fig- 1c: Pathophysiology of HLH



One of the greatest challenges in diagnosing secondary HLH is its considerable clinical overlap with sepsis, severe infections, autoimmune disease flares, macrophage activation syndrome, and hematological malignancies. Hyperferritinemia, although a key diagnostic marker, is not specific to HLH and may also be observed in sepsis, acute liver injury, adult-onset Still's disease, and malignancies. Therefore, ferritin should be interpreted in conjunction with other clinical and laboratory findings. The concurrent presence of persistent fever, cytopenias, hypertriglyceridemia, hypofibrinogenemia, hepatosplenomegaly, and evidence of hemophagocytosis substantially increases the likelihood of HLH. Accordingly, application of the HLH-2004 diagnostic criteria together with careful clinical assessment is essential for differentiating HLH from these mimicking conditions.

Table 2: Diagnostic criteria for HLH-2004 requiring five of eight clinical and laboratory parameters for diagnosis.

Diagnostic criteria for haemophagocytic lymphohistiocytosis (HLH)
A. Molecular diagnosis consistent with HLH
or
B. Diagnostic criteria for HLH fulfilled (5 of the 8 criteria below)
Fever
Splenomegaly
Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood)
Haemoglobin < 9 g/L
Neutrophils < 1.0×10^9 µ/L
Platelets < 100×10^3 µ/L
Hypertriglyceridaemia and/or hypofibrinogenaemia
Fasting triglycerides ≥ 3.0 mmol/L (i.e. ≥ 265 mg/dL)
Fibrinogen ≤ 1.5 g/L (i.e. ≤ 150 mg/dL)
Haemophagocytosis in bone marrow, spleen or lymph nodes
Low or no NK-cell activity
Ferritin ≥ 500 ng/L
sCD25 (i.e. soluble IL-2 receptor) ≥ 2400 U/mL

HLH: Hemphagocytic Lymphohistiocytosis, NK: natural killer.

Differential diagnosis

Secondary HLH shares several clinical and laboratory features with sepsis, severe systemic infections, autoimmune flare, macrophage activation syndrome (MAS), acute liver failure, thrombotic microangiopathy, and hematological malignancies. Consequently, differentiating HLH from these conditions requires careful integration of clinical presentation, laboratory findings, and the HLH-2004 diagnostic criteria.

Case 1: Persistent fever with positive blood culture initially suggested bacterial sepsis. However, persistent fever despite appropriate antibiotics, hepatosplenomegaly, cytopenias, markedly elevated ferritin, hypofibrinogenemia, and bone marrow hemophagocytosis fulfilled the HLH-2004 diagnostic criteria, supporting infection-triggered secondary HLH.

Case 2: The principal differential diagnoses included active systemic lupus erythematosus (SLE) flare, autoimmune hemolytic anemia (AIHA), macrophage activation syndrome (MAS), and infection. Although SLE accounted for the autoimmune manifestations, the coexistence of persistent fever, splenomegaly, cytopenias, Hyperferritinemia, hypofibrinogenemia, and hypertriglyceridemia was more consistent with secondary HLH occurring in association with SLE.

Case 3: Severe dengue infection alone can cause thrombocytopenia and hepatic dysfunction. However, persistent fever, marked Hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, progressive cytopenias, and multiorgan involvement strongly favoured dengue-associated secondary

HLH rather than uncomplicated severe dengue.

Although the final immunopathological pathway in HLH is characterized by excessive macrophage activation and a cytokine storm, the initiating mechanisms differ according to the underlying trigger. In Case 1, Pseudomonas aeruginosa bacteremia likely induced persistent activation of the innate immune system through pathogen-associated molecular patterns (PAMPs), resulting in sustained macrophage and cytotoxic T-cell activation with excessive cytokine release. Failure to adequately regulate this inflammatory response may have culminated in secondary HLH. In Case 2, systemic lupus erythematosus (SLE) with autoimmune hemolytic anemia (AIHA) created a state of chronic immune dysregulation characterized by persistent activation of autoreactive lymphocytes, immune complex formation, complement activation, and excessive cytokine production. These mechanisms predispose susceptible patients to macrophage activation syndrome; a form of secondary HLH associated with autoimmune diseases. In Case 3, severe dengue infection is known to trigger intense immune activation through direct viral stimulation of monocytes, macrophages, and T lymphocytes, resulting in marked production of pro-inflammatory cytokines including interferon-γ, tumour necrosis factor-α, and interleukins. This exaggerated immune response contributes to endothelial dysfunction, multiorgan involvement, and progression to dengue-associated secondary HLH. Despite the differing triggers, all three cases converged on a common pathway of uncontrolled immune activation, resulting in the characteristic clinical and laboratory manifestations of HLH [5–7,12–15].

The clinical laboratory plays a pivotal role in the early recognition of secondary HLH by identifying characteristic biochemical and hematological abnormalities that may precede definitive clinical diagnosis. In all three patients, routine laboratory investigations including complete blood counts, liver function tests, serum ferritin, fibrinogen, triglycerides, lactate dehydrogenase (LDH), and inflammatory markers provided the initial evidence of an underlying hyperinflammatory syndrome. Persistent cytopenias involving two or more cell lineages, marked hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia, and elevated liver enzymes should prompt clinicians to consider HLH, particularly in patients with persistent fever and multiorgan involvement. A stepwise laboratory approach beginning with complete blood count and inflammatory markers, followed by serum ferritin, triglycerides, fibrinogen, liver function tests, and bone marrow examination when clinically indicated, can facilitate early application of the HLH-2004 diagnostic criteria. Timely communication of these critical laboratory abnormalities between the laboratory and the treating clinicians is essential for prompt diagnosis, early initiation of immunosuppressive therapy, and improved clinical outcomes.

Recent evidence further supports serial monitoring of ferritin, triglycerides, fibrinogen, complete blood counts, liver function tests, and inflammatory markers for evaluating disease progression and response to therapy. Integration of these laboratory parameters with the HLH-2004 diagnostic criteria enables earlier recognition of HLH and facilitates prompt therapeutic intervention [13,14]. Additionally, Rosenbloom et al. demonstrated that in patients with Systemic Inflammatory Response Syndrome (SIRS), increased expression of CD11b and CD35 on polymorphonuclear neutrophils (PMNs) correlated with serum IL-6 levels and the severity of organ dysfunction, suggesting that PMN activation is linked to inflammation and organ failure in these patients [10]. Haddad E et al. noted that central nervous system (CNS) involvement frequently occurs in secondary HLH, often manifesting early with symptoms such as seizures and meningitis, and that bone marrow transplantation (BMT) performed after initial remission offers the best chance for halting CNS disease progression and achieving long-term remission [11]. Furthermore, advances in the understanding of HLH immunopathogenesis have resulted in the development of targeted therapies, including interferon-γ blockade and Janus kinase (JAK) inhibitors, particularly for patients with refractory or relapsed disease. Although corticosteroids and etoposide remain the standard initial therapy, these newer treatment strategies represent promising adjuncts in selected patients [15,16].

In summary, the integration of clinical, biochemical, and genetic findings is essential in diagnosing HLH, enabling timely intervention that can greatly enhance patient prognosis.

Table 3: HLH-2004 diagnostic criteria fulfilled by each patient.

HLH-2004 Criterion	Case 1	Case 2	Case 3
Fever	✓	✓	✓
Splenomegaly	✓	✓	✗
Cytopenias	✓	✓	✓
Hypertriglyceridemia	✗	✓	✓
Hypofibrinogenemia	✓	✓	✓
Ferritin ≥500 ng/mL	✓	✓	✓
Hemophagocytosis	✓	✗ (Not performed)	✗ (Not performed)
NK-cell activity	Not done	Not done	Not done
Soluble CD25	Not done	Not done	Not done
Criteria fulfilled	**6/8**	**6/8**	**5/8**

HLH-2004 diagnostic criteria fulfilled by the three patients. Diagnosis of secondary HLH was established according to the HLH-2004 guidelines, requiring fulfilment of at least five of the eight diagnostic criteria.

Conclusion

HLH represents a heterogeneous disorder with various underlying causes and is likely underdiagnosed, contributing to its significant morbidity and mortality. This case series describes three patients with secondary HLH, each arising from different triggers: a bacterial infection (Pseudomonas aeruginosa), an autoimmune condition (SLE with AIHA), and a viral infection (severe dengue). Laboratory tests play a critical role in diagnosing secondary HLH, with findings such as hyperferritinemia, elevated liver enzymes (aspartate transaminase [AST] and alanine transaminase [ALT]), hypertriglyceridemia, and hypofibrinogenemia, alongside histopathological confirmation through evidence of hemophagocytosis. Notably, hypofibrinogenemia was identified as a marker associated with poorer outcomes. Prompt recognition and management of the underlying causes are essential to improving prognosis in secondary HLH. Nevertheless, ongoing efforts are needed to enhance disease awareness and optimize treatment approaches for affected patients.

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Ethical clearance

According to institutional policy, ethical approval was waived by the Institutional Ethics Committee for this case series.

Written informed consent for publication was obtained from the legal guardian of the minor patient (Case 1) and from the adult patients (Cases 2 and 3) prior to inclusion in the study.
Ethical clearance is waived off for case reports by IEC, AIIMS Patna.

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None.

Conflict of interest

Authors declare no conflict of interest.

Author contributions

1. LPK, MM: conception or design of the work, acquisition, analysis, and interpretation of data for the work
2. LPK, SK, MM: analysis and interpretation of data,
3. LPK, MM: Drafting the work or revising it critically for important intellectual content
4. SK,RK,JP: providing clinically relevant samples for assay
5.RK,JP:Clinical management

All authors have approved of the final draft for publication purpose and are accountable for the accuracy and integrity of the work.

Supplementary material

No.
Informed consent was taken from patient concerned for publishing data and case details in a medical journal.

Data availability statement

All relevant data have been provided along with the manuscript.

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