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ENTERIC FEVER WITH MULTIPLE CO-INFECTIONS AND SUSPECTED HLH FOLLOWING APPENDICITIS: A RARE CLINICAL OVERLAP

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening syndrome defined by excessive immune activation and a hyperinflammatory response. It is classified into primary HLH, associated with genetic mutations, and secondary HLH, which is triggered by infections, malignancies, autoimmune diseases, or other systemic inflammatory conditions [1,2]. The pathophysiology involves excessive activation of macrophages and cytotoxic T-cells, leading to uncontrolled production of cytokines and multi-organ dysfunction [3].

Infections remain a major trigger for secondary HLH, with viral infections (such as Epstein-Barr virus (EBV) and dengue virus) being the most common causes [4,5]. However, bacterial infections like Salmonella Typhi (enteric fever) and Leptospira spp. (leptospirosis) have also been reported to precipitate HLH [6,7]. The clinical presentation is highly nonspecific, often mimicking sepsis or multi-organ failure, which makes early diagnosis challenging.

The HLH-2004 diagnostic criteria, proposed by the Histiocyte Society, require at least five out of eight criteria for diagnosis: fever, splenomegaly, cytopenia, hypertriglyceridemia or hypofibrinogenemia, hyperferritinemia, hemophagocytosis, low NK cell activity, and elevated soluble CD25 (sCD25) levels [8]. Given its high mortality, early recognition and initiation of treatment, typically with immunosuppressive therapy such as dexamethasone and etoposide, are critical [9].

We report a unique case of HLH in a young male who initially presented with fever, gastrointestinal symptoms, and acute appendicitis but later developed worsening systemic inflammation due to concurrent infections with Salmonella Typhi, Leptospira, and suspected dengue fever. This case highlights the diagnostic complexity of HLH in the context of multiple infectious triggers and emphasizes the importance of early multidisciplinary intervention.

Case Presentation

A 24-year-old previously healthy male arrived at the hospital with a one-week history of fever that began insidiously; it was intermittent and low-grade, accompanied by chills and rigors. Over the past three days, he developed persistent vomiting and diarrhea, with each occurring three times a day. His symptoms worsened, presenting as a diffuse, throbbing headache that wouldn't subside, making him feel progressively weaker and more fatigued.

The Unexpected Diagnosis:

Initial laboratory tests showed normal hematological parameters, except for mild thrombocytopenia (Platelet count: 1.28 lakh/µL) and a total leukocyte count of 4510/µL. The liver function tests (LFTs) indicated elevated bilirubin levels (Total: 2.26 mg/dL, Direct: 1.74 mg/dL) and increased liver enzymes (AST: 139 U/L, ALT: 54 U/L, GGT: 172 U/L). Renal function and electrolytes were within normal limits.

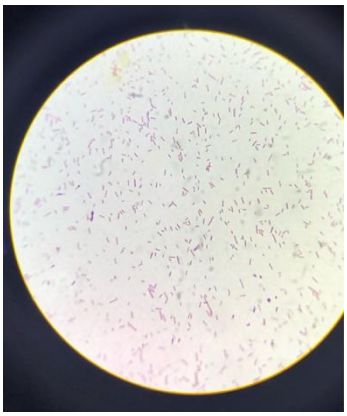
Test Type	Parameter	Result	Normal Range
Hematological	Platelet count	1.28 lakh/µL	Decreased
Hematological	Total leukocyte count	4510/µL	Normal
Liver Function	Total bilirubin	2.26 mg/dL	Elevated
Liver Function	Direct bilirubin	1.74 mg/dL	Elevated
Liver Function	AST	139 U/L	Elevated
Liver Function	ALT	54 U/L	Elevated
Liver Function	GGT	172 U/L	Elevated
Renal Function	Renal function and electrolytes	Within normal limits	Normal

Given his ongoing fever and gastrointestinal symptoms, a CT of the abdomen was performed, which surprisingly revealed acute appendicitis along with hepatosplenomegaly. The patient was immediately prepared for a laparoscopic appendectomy under general anaesthesia on January 6, 2025.

A Mysterious Turn of Events:

The surgery was uneventful, and the patient was transferred to the Intensive Care Unit (ICU) for post-operative monitoring. However, within 24 hours, his condition deteriorated—his fever persisted, and he began showing signs of worsening systemic inflammation.

Alarm bells rang when his repeat blood cultures grew *Salmonella Typhi* from both upper limbs, confirming enteric fever. Meanwhile, his Leptospira IgM returned positive, adding another infectious etiology to the mix. The patient’s platelet count dropped further, and his liver function tests (LFTs) worsened, showing signs of progressive hepatic dysfunction.



Salmonella typhi- Gram negative- rod shaped bacteria under microscope.

Flow Chart: Timeline of Events

Presentation
(January 6, 2025)
▼
Laparoscopic Appendectomy
▼
Post-operative Condition
(Persistent fever, inflammation)
▼
Blood Cultures Positive
(Salmonella Typhi, Leptospira IgM positive)
(January 7, 2025)
▼
Further Clinical Condition
Additional Investigations Conducted
(January 8-10, 2025)

Unraveling a Deeper Mystery:

As concerns grew, a comprehensive workup was initiated, revealing:

Condition	Details
Severe hyperferritinemia	>1000 ng/mL
Elevated serum amylase	696 U/L
Elevated serum lipase	7927 U/L
Dyslipidemia	Low HDL: 17 mg/dL, TG: 354 mg/dL
Mild coagulopathy	Fibrinogen level: 416 mg/dL
MRCP	Perihepatic fluid collection, Mild pleural effusion

With worsening cytopenia, hepatosplenomegaly, hyperferritinemia, and persistent fever, the suspicion of Hemophagocytic Lymphohistiocytosis (HLH) arose. A rheumatology consultation was sought, and hematology experts advised serial CBC and ferritin monitoring. If cytopenia and hyperferritinemia persisted, a bone marrow aspiration/biopsy (BMA/BMB) would be planned.

Battling on Multiple Fronts:

Recognizing the complexity of the case, a multidisciplinary team was involved. The patient was placed on a broad-spectrum antibiotic regimen that included:

Medication	Dosage	Route	Frequency
Meropenem	1g	IV	TDS
Cefoperazone-Sulbactam	1.5g	IV	BD
Azithromycin	500mg	PO	OD
Doxycycline	100mg	PO	BD

Supportive therapy included paracetamol for fever, ondansetron for nausea, hepatic support with Hepamerz sachets and Ursodeoxycholic acid (Udiliv), and Fresh Frozen Plasma (FFP) transfusions to manage coagulopathy.

The Diagnostic Conundrum:

The case presented a diagnostic dilemma: was the worsening inflammation solely due to concurrent infections, or was the patient developing infection-associated HLH, a rare but life-threatening condition? The patient met several HLH-2004 diagnostic criteria, but confirmation awaited bone marrow findings.

Over the following days, serial monitoring continued, and the patient's fever gradually subsided, platelet counts stabilised, and liver enzymes showed signs of recovery. While HLH remained a strong possibility, aggressive antimicrobial therapy and supportive management led to gradual improvement, thus preventing the need for immunosuppressive therapy.

A Lesson in Complexity

This case highlights the diagnostic challenges presented by overlapping infectious syndromes in a critically ill patient. With multiple coexisting infections—enteric fever, leptospirosis, and suspected dengue—and a potential hyperinflammatory response, early suspicion of HLH and a multidisciplinary intervention were crucial in preventing catastrophic progression.

Final Diagnosis

1. Enteric Fever (*Salmonella Typhi* Bacteremia)
2. Acute Appendicitis (Post-Laparoscopic Appendectomy)
3. Leptospirosis
4. Suspected Dengue Fever
5. Possible Infection-Associated Hemophagocytic Lymphohistiocytosis (HLH)

This case underscores the importance of early suspicion, aggressive infection management, and close monitoring when facing a potential cytokine storm in a critically ill patient.

Discussion

This case illustrates a complex diagnostic challenge, where a 24-year-old male presented with a constellation of infectious and inflammatory manifestations, ultimately raising suspicion for Hemophagocytic Lymphohistiocytosis (HLH). The simultaneous presence of enteric fever, leptospirosis, and suspected dengue created a perfect storm of immune dysregulation, making early diagnosis and management crucial. This case underscores the critical role of early recognition and multidisciplinary intervention in infection-associated HLH.

HLH: A Deadly Cytokine Storm

HLH is a life-threatening hyperinflammatory syndrome characterized by dysregulated immune activation. It can be primary (genetic mutations affecting cytotoxic T-cell and NK-cell function) or secondary

(triggered by infections, malignancies, or autoimmune conditions) [10,11]. The underlying pathology involves excessive activation of macrophages and T-cells, leading to a cytokine storm (IL-6, IFN-γ, TNF-α, IL-18, soluble IL-2 receptor) and uncontrolled tissue damage [12]. The clinical overlap between severe systemic infections and HLH makes diagnosis challenging, often resulting in delayed or missed recognition.

The HLH-2004 criteria, established by the Histiocyte Society, require at least five out of eight parameters for diagnosis [13]:

1. Prolonged fever >38.5°C
2. Splenomegaly
3. Cytopenias (affecting ≥2 lineages: Hb <9 g/dL, Platelets <100,000/μL, Neutrophils <1,000/μL)
4. Hypertriglyceridemia (>265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, or lymph nodes
6. Hyperferritinemia (>500 ng/mL, often >10,000 ng/mL in severe cases)
7. Elevated soluble IL-2 receptor (sCD25)
8. Decreased or absent NK cell activity

Our patient exhibited persistent fever, hepatosplenomegaly, worsening thrombocytopenia, hyperferritinemia (>1000 ng/mL), hypertriglyceridemia (TG: 354 mg/dL), and fibrinogen alterations, all strongly suggestive of HLH. However, bone marrow examination (BME) was still pending, and sCD25 was unavailable, which made definitive diagnosis difficult. This case exemplifies the importance of clinical suspicion and serial monitoring when HLH is suspected in critically ill patients.

The Role of *Salmonella Typhi* in HLH: An Uncommon Culprit

Enteric fever, caused by *Salmonella Typhi*, is a systemic bacterial infection that primarily affects the gastrointestinal and hepatobiliary systems. While it typically presents with fever, abdominal pain, hepatosplenomegaly, and bacteremia, its role in triggering HLH remains underreported [14,15].

Salmonella spp. can trigger a hyperinflammatory immune response via Toll-like receptor (TLR) activation, macrophage stimulation, and the excessive release of IL-6, IL-1, and TNF-α. This inflammatory cascade may result in hemophagocytosis and immune dysregulation, resembling HLH [16].

A systematic review of *Salmonella*-induced HLH found that most cases presented with prolonged fever, worsening cytopenia, and hepatosplenomegaly, and a mortality rate of 25-50% when diagnosis was delayed [17]. Our patient demonstrated these features with positive blood cultures for *Salmonella Typhi* and worsening hematological parameters, emphasizing the need for early suspicion and treatment.

Leptospirosis and HLH: A Rare but Lethal Combination

Leptospirosis, a zoonotic spirochetal disease, is rarely associated with HLH; however, severe cases can trigger macrophage activation and cytokine dysregulation, mimicking HLH [18]. *Leptospira* spp. induce a profound inflammatory response driven by lipopolysaccharide (LPS)–mediated activation of macrophages and endothelial dysfunction [19].

A retrospective study of HLH secondary to leptospirosis reported that patients often exhibit high ferritin levels (>1000 ng/mL), thrombocytopenia, and transaminitis, as observed in our patient [20]. The challenge lies in distinguishing HLH from severe leptospirosis with hemophagocytosis, as administering immunosuppressive therapy (steroids, etoposide) in an untreated infection can be fatal [21].

Our patient tested positive for Lepto-IgM and presented with hepatosplenomegaly, thrombocytopenia, and hyperferritinemia, indicating possible leptospirosis-associated HLH. However, his gradual recovery with antimicrobial therapy alone suggests that the immune activation was driven by the infection rather than primary HLH, reinforcing the need for careful clinical judgment in such cases.

Dengue-Associated HLH: A Recognised but Overlooked Phenomenon

Dengue fever is one of the most well-established viral triggers of HLH, particularly in endemic regions [22]. Dengue-associated HLH results from overactivation of T-cells and macrophages, leading to a cytokine storm (IL-6, IFN-γ, TNF-α, IL-18) [23].

A meta-analysis of dengue-associated HLH found that hyperferritinemia (>10,000 ng/mL) and persistent cytopenias were associated with poor outcomes [24]. While our patient's dengue status remained unconfirmed, his thrombocytopenia, hyperferritinemia, and persistent fever raised suspicion. Supportive care and close monitoring were key to preventing disease progression.

Conclusion

This case highlights the diagnostic complexity and clinical dilemma of distinguishing severe infections from hemophagocytic lymphohistiocytosis (HLH). A young male presented with fever, thrombocytopenia, hepatosplenomegaly, and worsening inflammatory markers that initially suggested common tropical infections—enteric fever, leptospirosis, and suspected dengue. However, his persistent fever, hyperferritinemia, and worsening cytopenias heightened suspicion for infection-triggered HLH, a potentially fatal hyperinflammatory syndrome if not identified and managed promptly.

In this case, the coexistence of enteric fever, leptospirosis, and suspected dengue created a perfect storm of immune dysregulation, making early recognition critical. *Salmonella Typhi*, an uncommon trigger of HLH, resulted in persistent bacteremia, worsening cytopenias, and progressive liver dysfunction. Leptospiral infection exacerbated the inflammatory cascade, further driving cytokine overproduction and immune activation. Meanwhile, dengue-associated thrombocytopenia and hyperferritinemia blurred the diagnostic boundaries, emphasizing the importance of serial monitoring and multidisciplinary input in such cases.

This case reinforces several key lessons:

1. **HLH should consistently be considered in critically ill patients presenting with persistent fever, hepatosplenomegaly, and cytopenias, particularly in cases of tropical infections.**
2. **Not all HLH cases require immunosuppression; some are infection-driven and may resolve with appropriate antimicrobial therapy.**
3. **Serial monitoring of ferritin, cytopenias, and inflammatory markers is crucial for distinguishing between severe sepsis, HLH, and overlapping syndromes.**
4. **Timely collaboration among infectious disease specialists, hematologists, and intensivists is essential for guiding treatment decisions.**

Ultimately, this case serves as a cautionary tale—HLH is often a misdiagnosed condition in infectious disease settings, leading to delayed treatment and high mortality rates. Increasing awareness, early recognition, and personalized management strategies can significantly impact patient outcomes, potentially making the difference between life and death.

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