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Case Series

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Beyond the Usual Suspects: A Case Series of Atypical Infectious Etiologies in HLH

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome characterized by uncontrolled immune activation, posing diagnostic and therapeutic challenges. A previously healthy 12-year-old girl presented with fever and worsening jaundice, revealing transaminitis and positive hepatitis A IgM. Initial management led to improvement, but subsequent fever, bicytopenia, and hyperferritinemia prompted bone marrow examination, confirming HLH. Dexamethasone treatment resolved fever and improved pancytopenia within five days. A 41-year-old woman presented with fever, respiratory symptoms, abdominal distension, and pedal edema. Despite negative serological tests, leptospira infection was confirmed. Failure of treatment prompted bone marrow examination revealing hemophagocytosis. Elevated triglycerides, ferritin, and decreased fibrinogen confirmed HLH. Treatment with intravenous methylprednisolone led to significant improvement in lab and hematological parameters. This case series highlights two distinct presentations of HLH, emphasizing the diversity of its clinical manifestations and the critical need for prompt recognition and management.

Introduction

Hemophagocytic Lymphohistiocytosis (HLH) is a severe hyperinflammatory condition that arises in individuals with genetic anomalies, hematologic cancers, chronic inflammation, or infections. Key clinical hurdles include identifying HLH, discerning whether the immune response is abnormal or appropriate, and selecting suitable treatment. Recognizing HLH proves daunting due to its symptomatic overlap with various systemic disorders, necessitating keen suspicion and timely diagnostic efforts to confirm the condition and pinpoint its underlying

cause. In this report, we present a case series detailing two unusual infectious origins of HLH, which posed diagnostic challenges.

Case Series

Case 1

A previously healthy 12-year-old female presented with a four-day history of fever followed by worsening jaundice, accompanied by abdominal pain, nausea, and reduced oral intake. Physical examination revealed icteric skin, tenderness in the right upper quadrant of the abdomen, and a palpable liver 2 cm below the costal margin. No signs of hepatic encephalopathy or bleeding were noted. Laboratory investigations showed normal complete blood count and kidney function tests, but significant transaminitis with elevated SGOT and SGPT levels (7873 IU/ml and 9750 IU/ml, respectively), along with a total bilirubin of 5.2 mg/dl and an INR of 3.01. Hepatitis panel testing revealed positive hepatitis A IgM, while other viral markers were negative. Conservative management with intravenous fluids led to clinical and laboratory improvement. However, after four days, the patient developed fever again, along with progressive bicytopenia (Hb 8.6 g/dl & TLC 1760/mm^3), hyperferritinemia (3971 ng/ml), and hypertriglyceridemia (437 mg/dl). The investigation trend is mentioned in the following **Table 1**. No splenomegaly or hypofibrinogenemia was observed while bone marrow examination demonstrated hemophagocytosis **(Figure 1)**, yielding an H-Score of 249 (>99% probability of HLH). Treatment with Dexamethasone 10 mg/m^2 once daily resulted in fever resolution within five days and improvement of pancytopenia.

Table 1: Investigation trend during the hospital stay.

LABORATORY FINDINGS	DAY 1	DAY 5	DAY 10	DAY 15
Hemoglobin g/dl	12.2	**8.6**	9.8	10.1
Leukocytes, 10^9/L	6260	**1760**	7150	8250
Platelet counts, 10^9/L	186	206	256	243
Total bilirubin, mg/dl (normal 0– 1.2)	5.2	4.9	3.2	1.8
Direct bilirubin, mg/dl (normal 0– 0.5)	4.2	3.8	2.1	1.3
AST, IU/L (normal 5– 34)	9873	1693	384	113
ALT, IU/L (normal 0– 55)	9750	3260	483	156
INR	3.01	1.96	1.2	0.98
Ferritin ng/ml		**3971**		347
Triglyceride mg/dl		**437**		225
Fibrinogen, mg/dl		391	360	382

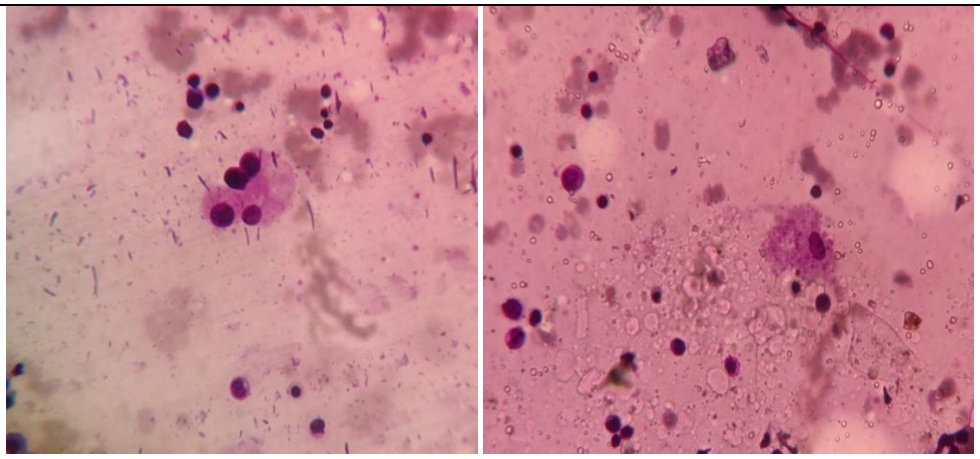

Figure 1: Bone marrow aspiration demonstrate multiple foci of hemophagocytosis.

Case 2

A 41-year-old woman presented with a four-day history of fever, shortness of breath, dry cough, abdominal distension, pedal edema, facial puffiness, and decreased urine output. There were no reports of chest pain, orthopnea, paroxysmal nocturnal dyspnea, joint pain, abdominal pain, yellowish discoloration, or bleeding. On examination, she was febrile, tachypneic (34 per minute), with bilateral pitting pedal edema, hepatosplenomegaly, and bilateral inspiratory crepitations. Blood tests indicated bicytopenia, leukocytosis, deranged liver and kidney functions, and metabolic acidosis **(Table 2)**. Chest X-ray revealed diffuse fluffy, inhomogeneous airspace opacities in bilateral lung fields, predominantly in lower zones. Serological tests for various infections, including malaria, dengue, scrub typhus, enteric fever, chikungunya, and hepatitis, were negative, as were the autoimmune workup, rheumatoid factor and HIV status. However, leptospira PCR and IgM by ELISA were positive. Despite treatment with ceftriaxone and doxycycline for five days, there was no improvement. To investigate potential alternative or additional causes of persistent bicytopenia, a bone marrow examination was performed. The examination revealed normal erythroid and myeloid lineages, adequate megaloblasts, and an absence of granulomas, hemoparasites, or atypical cells. However, histiocytes were present with evidence of hemophagocytosis **(Figure 2)**. She had elevated triglyceride levels (614 mg/dL), ferritin (5480 ng/mL), and decreased fibrinogen (54 mg/dL). The H-score was 210, prompting treatment with pulse dose intravenous methylprednisolone 500 mg for three days, followed by oral maintenance. The patient responded well to treatment, with normalization of lab parameters, including liver and kidney functions, and gradual improvement in hematological parameters.

Table 2: Investigation trend during the hospital stay.

Parameters	Day 1	Day 5	Day 6	Day 10	Day 15
Hb	5.8 g/dl	6.1	5.9	7.0	8.4
TLC	16210	18100	15400	11200	9600
Plt	65000	48000	35000	87000	145000
ESR	136 mm/hr				
Total Bilirubin	3.6	3.4	3.5	2.6	2.1
ALT	93 U/L	104	116	78	35
AST	187 U/L	125	187	65	47
ALP	980 U/L				
Urea	169mg/dl	145	152	104	78
Creatinine	4.1 mg/dl	4.5	5.2	3.9	2.0
Ferritin			**5480 ng/mL**		
S. Fib			**54 mg/dL**		
Triglyceride			**614 mg/dL**		
Ddimer			**3870**		

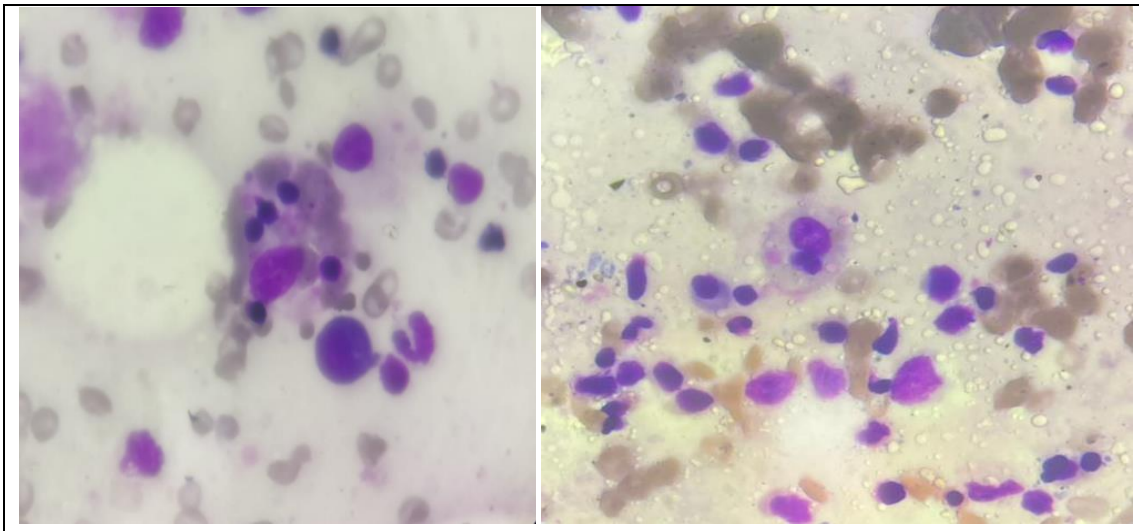

Figure 2: Bone marrow aspiration demonstrate multiple foci of hemophagocytosis.

Discussion

HLH represents a severe condition characterized by dysregulated immune activity and hyperinflammation, driven by the activation of cytotoxic T lymphocytes and macrophages. Traditionally, HLH has been classified into primary/familial (F-HLH) and secondary/sporadic/reactive forms. F-HLH arises from heritable genetic mutations impacting cytolytic functions, lymphocyte survival, or inflammasome activation, while secondary HLH can stem from various causes including infections, malignancies, autoimmune disorders, and immunodeficiency states **[1]**. In the context of rheumatological diseases, HLH is often termed Macrophage Activation Syndrome (MAS). Although the exact prevalence of HLH remains uncertain, estimates indicate it affects approximately 1-3 individuals per million annually, with secondary HLH being more common. A review

suggests a mean age of diagnosis at 49 years, with a male-to-female ratio of 1.7:1 [2,3]. HLH pathogenesis hinges on hypercytokinemia, initiated by triggers like infections and tumors. These triggers activate CTL and NK cells, prompting the release of perforin and granzyme B, which induce apoptosis in target cells. Simultaneously, a cascade of cytokines including interferon-gamma, TNF-alpha, IL-6, and colony-stimulating factors, heightens macrophage activity in the bone marrow. In secondary HLH, macrophages are spurred by underlying immunogenic factors [4]. Hypercytokinemia triggers prolonged fever and fatigue, while downregulation of CD47 expression on hematopoietic cells disrupts self-recognition mechanisms, favoring phagocytosis. Consequently, activated macrophages engulf various cells, including erythrocytes, leukocytes, platelets, and lymphoma cells lacking CD47, contributing to the cytopenias characteristic of HLH [5].

The diagnostic guidelines for haemophagocytic lymphohistiocytosis (HLH), initially proposed by the Histiocyte Society in 1991 and updated in 2004 and 2009, are widely utilized in adults [6-8]. These criteria encompass clinical, laboratory, and histopathological parameters. Clinical features consist of fever (>38.5°C), hepatosplenomegaly, lymphadenopathy, and cytopenias affecting at least two of three lineages. Laboratory findings include elevated ferritin levels (>500 µg/L), elevated soluble CD25 levels (>2,400 U/mL), reduced or absent NK-cell activity, elevated triglycerides (>265 mg/dL) and/or low fibrinogen (<150 mg/dL), or evidence of hemophagocytosis in bone marrow, spleen, or lymph nodes. Diagnosis is established if any of these criteria are met [7]. The 2009 revision aimed to streamline diagnostic criteria while maintaining accuracy, reflecting advancements in understanding HLH pathophysiology and genetics. Incorporating genetic testing and additional laboratory parameters enhances diagnostic accuracy and allows for earlier intervention, thereby improving patient outcomes. The differences between the 2004 and 2009 criteria are outlined in the following **Table 3**. Nonetheless, a high degree of clinical suspicion remains crucial for timely HLH diagnosis [8].

Table 3: Important differences between the two criteria.

	HLH 2004	HLH 2009
Genetic Testing	Genetic testing was not included in the initial criteria.	Incorporates genetic testing, especially for familial HLH.
NK Cell Activity	Not explicitly included as a diagnostic criterion.	Requires demonstration of reduced or absent NK cell activity.
CD25 (sIL-2R) Levels	Not part of the initial criteria.	Elevated soluble CD25 (sIL-2R) levels (>2,400 U/mL) are included.
Triglyceride/Fibrinogen Levels	Not specified in the 2004 criteria.	Elevated triglycerides (>265 mg/dL) and/or low fibrinogen (<150 mg/dL) are considered.
Diagnostic Algorithm	Follows a stepwise approach with sequential testing.	Integrates various parameters simultaneously for diagnosis.

Infections and HLH

Infectious agents play a significant role in precipitating HLH, with a diverse array of pathogens implicated in its pathogenesis. Viral infections constitute the most common etiology, occurring either as primary infections in immunocompetent individuals or through reactivation in immunosuppressed patients. Notably, 43% of viral

HLH cases are attributed to Epstein Barr virus (EBV), followed by 9% to Cytomegalovirus (CMV). Additionally, cases of HLH have been reported following infections with parvovirus B19, influenza, and SARS-COV2 [4]. Bacterial infections account for 9% of adult HLH cases, with tuberculosis responsible for 38% of these cases. Furthermore, HLH has been associated with adjuvant intravesical or BCG vaccination, as well as infections by Rickettsia, Staphylococcus, and Escherichia coli [9]. Parasitic and fungal triggers are less common, with Histoplasma, Leishmania, Plasmodium, and Toxoplasma being among the frequently reported pathogens. A thorough travel history is essential in identifying the triggering agent, particularly in immunocompetent patients returning from endemic regions. In immunosuppressed individuals, HLH is often linked to opportunistic infections such as Pneumocystis jiroveci, Toxoplasma gondii, and various fungi [10]. Beyond conventional pathogens, atypical infections pose a distinctive yet increasingly recognized association with HLH. Emerging evidence delineates the role of uncommon microbes in precipitating HLH, thereby expanding the spectrum of infectious triggers. These infections often elude routine diagnostic algorithms, necessitating a heightened index of suspicion in the context of unexplained HLH presentations [5]. HLH secondary to Hepatitis A Virus (HAV) infection is rarely documented in the existing literature, particularly among adults. Mallick et al. reported an uncommon case of HLH associated with HAV infection in a 21-year-old man, complicated by hemolysis due to G-6-PD deficiency and fungal sepsis. Treatment included Intravenous Immunoglobulin (IVIg) and supportive care [11]. Dogan et al. [12] described a similar case characterized by persistent fever, pancytopenia, splenomegaly, hyperferritinemia, and hemophagocytosis in the bone marrow, with successful treatment using IVIG and dexamethasone. Bay et al. [13] reported two cases of HLH secondary to Hepatitis A infection in the pediatric population. Virus-Associated Hemophagocytic Syndrome (VAHS) is a critical condition with diverse clinical features. It should be considered in patients presenting with hepatitis, unresponsive fever, and cytopenia. VAHS can affect both pediatric and adult populations infected with Hepatitis A Virus (HAV), with most cases identified during the index hospitalization. However, delayed diagnosis, up to 2–6 weeks after resolution of initial hepatic symptoms, has been reported. Underlying autoimmune conditions may increase the risk of HAV-induced VAHS. Fever is consistently present, with thrombocytopenia being a prominent feature among cytopenias [11]. Leptospirosis is an even rarer cause of secondary HLH than HAV. Through extensive research, we have found limited mentions on this topic. Munasinghe et al. [14] reported a case of a 74-year-old male diagnosed with leptospirosis who developed unresolving fever, hepatosplenomegaly, and pancytopenia. Despite the addition of IVIg and steroids, the patient succumbed to the illness, with a bone marrow biopsy and markedly elevated serum ferritin and triglyceride levels confirming the diagnosis of HLH. Similarly, Barman et al. [15] described a case of a 40-year-old male with leptospirosis and secondary hemophagocytosis presenting with high-grade fever and jaundice. Despite aggressive management, including IVIg and steroids, the patient experienced multi-organ dysfunction and eventually passed away.

Conclusion

In summary, secondary HLH encompasses a diverse array of triggers, with infections occupying a prominent position in its pathogenesis. While conventional pathogens such as viruses and bacteria remain principal instigators, atypical infections like hepatitis A and leptospira merit attention as potential precipitants of HLH. Vigilance toward these diverse microbial culprits is imperative for expeditious diagnosis and therapeutic intervention in HLH, underscoring the intricate interplay between infectious agents and immune dysregulation.

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