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Case Series

INFECTIOUS DISEASES COMPLICATED BY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS – A RARE CASE SERIES

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a rare, yet potentially fatal disorder of uncontrolled inflammation and dysregulated immunity. Patients may present with features ranging from fever, rash, and cytopenias to fatal multiorgan failure. Here, we present a case series reporting four cases of HLH, their clinicopathological findings, laboratory investigations, and outcomes. The underlying causes for the four cases were found to be infective ones, i.e., *Leptospira*, hepatitis-E and herpes simplex virus-1, kala-azar and malaria and enteric fever. HLH is a manifestation of the dysregulated immune response of various T cells leading to cytokinemia causing an accumulation of macrophages and T lymphocytes in various tissues. Infections account for about half of all HLH cases in adults the world over. In our institute, infections may still be more prevalent as a cause. Moreover, this may be the scenario in our country where infectious diseases remain a major proportion of the disease burden.

Keywords: Hemophagocytic lymphohistiocytosis, Immunology, Hematology.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyper-inflammatory and immune dysregulation syndrome that leads to hypercytokinemia and aberrant activation of lymphohistiocytes and macrophages [1-3].

Based on the etiology, HLH may be as follows (Table 1):

- Primary/genetic (familial or associated with immune deficiency syndromes)
- Secondary/acquired (most common trigger being Epstein–Barr virus).

The clinical manifestations are usually non-specific such as fever, jaundice, rash, hepatosplenomegaly, and cytopenias – most of which may be found in various infective as well as non-infective diseases, making the diagnosis a challenge [2,3]. The diagnosis of hemophagocytosis is based on the diagnostic criteria laid down by the histiocyte societies HLH study group (Table 2) [3,4].

HLH triggers include infections. The Indian subcontinent is home to a variety of tropical infections such as leptospirosis, dengue, chikungunya, malaria, kala-azar, enteric fever, and hepatitis-causing viruses which may have overlapping clinical features. A variety of microbes, including bacterial, viral, parasitic, and fungal agents, may set off HLH. Infection results in lymphohistiocytosis through the hyperproliferation and activation of T cells. There is proliferation of CD8+ cytotoxic T cells. This induces cytokinemia resulting from the abnormal activation of the immune system [5].

In our setup, infections have been found to be the most common cause of secondary HLH. This is a case series of four patients who were diagnosed with hemophagocytic lymphohistiocytosis. In this case series, all four cases had in common the chief complaint of high-grade fever, with associated variable symptoms, and the presence of hepatosplenomegaly on examination. These cases were initially managed as manifestations of an underlying tropical infection until the diagnosis of HLH was made. Post that, they were effectively treated with corticosteroids and achieved remission.

CASE 1

A 30-year-old male, non-alcoholic, with no previous co-morbidities, native of Punjab, who recently migrated to Bangalore (1 month ago), presented to the emergency with complaints of loss of appetite, fever, and loose stools for 10 days. This was followed by yellowish discoloration of both eyes and skin, highly colored urine, along with pain abdomen, nausea, vomiting, and exertional breathlessness.

Blood pressure was 90/60 mmHg, pulse rate was 110 beats/min, and SpO_2 was 93%. The patient was febrile, anemic, and icteric. There is no clubbing/cyanosis/edema/lymphadenopathy. Per abdomen showed tenderness+over right hypochondrium, hepatomegaly (liver span ~ 19 cm on percussion, soft, non-nodular), and splenomegaly. The rest of the examination was unremarkable.

The patient was stabilized, shifted to the intensive care unit, and put on inotropes and oxygen inhalation. Tests for the malarial parasite, dengue, and typhoid were negative. Peripheral blood smear revealed severe pancytopenia and hemolysis (Table 3). Blood and platelet transfusions were given.

Ultrasound (USG) whole abdomen revealed hepatosplenomegaly. Chest X-ray showed diffuse infiltrations. The patient also gave a history of contact with rats and unhygienic practices in the common kitchen. Serology for hepatitis A immunoglobulin (Ig)M was negative while that for hepatitis E virus (HEV) IgM and *Leptospira* IgM were positive.

The patient was started on the tablet doxycycline and injection ceftriaxone. Herpes simplex virus-1 (HSV-1) IgM also turned out positive. He was started on valacyclovir for the same. Despite adequate treatment for 7 days, the patient remained febrile, and blood counts were persistently low. Bone marrow examination was done suggestive of hemophagocytosis (Fig. 1) on the smear. S. ferritin was 7393 ng/mL, triglycerides were 490 mg/dL, and fibrinogen was 319 mg/dL.

Six out of eight criteria for HLH were met and the diagnosis of secondary HLH due to hepatitis E, leptospirosis, and HSV-1 was made. Accordingly, intravenous dexamethasone was started along with antibiotics and the patient started responding.

He was discharged on oral dexamethasone, ursodeoxycholic acid, and antibiotics. During the course of steroids, the patient developed dry cough and rhinitis and he turned out COVID-19 positive on reverse transcriptase-polymerase chain reaction, owing to his compromised immunity. He was readmitted and treated symptomatically and home isolated once his symptoms resolved.

Case 2

A 57-year-old diabetic male with a recent visit to Canada (1.5 months ago) presented in the outpatient department (OPD) of our hospital with chief complaints of high-grade fever associated with chills and rigors of 20-day duration. This was followed by vomiting, yellowish discoloration of eyes and skin, and highly colored urine. The patient had moderate-grade fever and an oxygen saturation of 92%. Icterus was present. Abdominal examination showed an enlarged liver (17 cm span, tender, soft, and non-nodular) along with a palpable spleen.

Table 1: Causes of HLH [3-5]

Genetic
Familial HLH 1–5
Immune deficiency syndromes
Griscelli syndrome
Chediack higashi
Hermansky pudlack II
Acquired
Infectious agents
Autoimmune syndromes
Malignant diseases
Organ transplantation

HLH: Hemophagocytic lymphohistiocytosis

Table 2: HLH Diagnostic Criteria 2009 [3,4]

1. Molecular diagnosis of HLH or X-linked lymphoproliferative syndrome
2. Or at least 3 of 4:
Fever (>38.5°C)
Splenomegaly
Cytopenias (minimum two cell lines reduced)
Hepatitis
3. And at least 1 of 4:
Hemophagocytosis in bone marrow or spleen, liver, lymph node
Raised ferritin (>500 ng/mL)
Raised slL-2 R* (CD25 concentration>2400 IU/mL)
Absent or very decreased NK cell function (measured by CD 107)
4. Other results supportive of HLH diagnosis:
Hypertriglyceridemia (>265 mg/dL)
Hypofibrinogenemia (<1.5 g/L)
Hyponatremia

HLH: Hemophagocytic lymphohistiocytosis

Table 3: Case 1 investigations

Laboratory parameter	Value
Hemoglobin (g/dL)	4.3
Total leukocyte count (/mm^3)	2440
Differential leukocyte count (%)	38(N)/53(L)
Platelets (/mm^3)	12,000
Creatinine (mg/dL)	0.6
Bilirubin (mg/dL)	18 (D-15.6)
AST/ALT/ALP	353/76/193
INR	1.69
S. Na/K (mEq/L)	130/4.1
HIV/HbsAg/Anti-HCV	NR/NR/NR
S. Amylase/S. Lipase	WNL
SFOB	Positive

ALP: Alkaline phosphatase, ALT: Alanine transaminase, AST: Aspartate aminotransferase, HbsAg: Hepatitis B surface antigen, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus, INR: International normalized ratio

The patient was managed in the OPD of our hospital. Tests for malarial parasite, chikungunya, hepatitis A and E, and scrub typhus were negative. Enteric fever was detected through positive IgM and IgG antibodies. Peripheral blood smear revealed normocytic normochromic red blood cells (RBCs), leukopenia, and thrombocytopenia with no hemoparasite (Table 4).

USG whole abdomen revealed hepatosplenomegaly with a thickened and edematous gallbladder wall. Chest X-ray showed a slight increase in brochovascular markings.

Bone marrow biopsy showed hypercellular marrow with a myeloid to erythroid ratio to be 2.4:1 with some megaloblastic change. Due to no improvement, a repeat bone marrow examination was carried out at our hospital which revealed hemophagocytosis (Fig. 2) on the smear. Serum ferritin was 911 ng/mL. The patient was started on a tablet of prednisolone 10 mg OD with an injection of amikacin 500 mg once daily for 5 days. Five out of eight criteria for HLH were met and the diagnosis of secondary HLH due to enteric fever was made.

Case 3

A 31-year-old border security force (BSF) soldier, a native of Jharkhand, with a recent visit to his native place presented to the BSF base hospital with chief complaints of high-grade fever associated with chills and rigors of 2-day duration. There were no associated complaints. His peripheral blood film showed trophozoites of *Plasmodium vivax*. He was started on

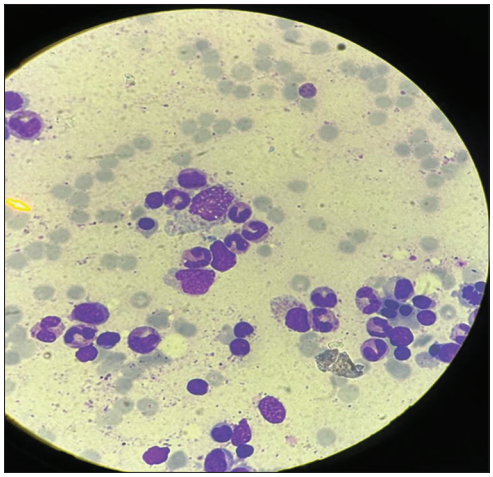

Fig. 1: Bone marrow smear from case 1

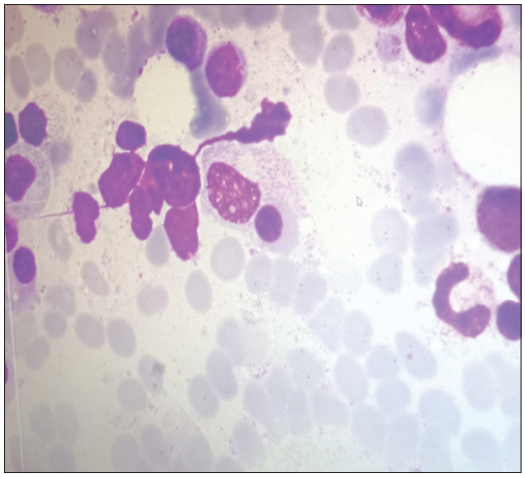

Fig. 2: Bone marrow smear from case 2

Table 4: Case 2 investigations

Laboratory parameter	Value
Hemoglobin (g/dL)	11.1
Total leukocyte count (/mm^3)	3550
Differential leukocyte count (%)	47(N)/43(L)
Platelets (/mm^3)	86,000
Creatinine (mg/dL)	0.7
Bilirubin (mg/dL)	7.2 (D-6)
AST/ALT/ALP	144/111/240
INR	1.45
S. Na/K (mEq/L)	126/4
HIV/HbsAg/Anti-HCV	NR/NR/NR

ALP: Alkaline phosphatase, ALT: Alanine transaminase, AST: Aspartate aminotransferase, HbsAg: Hepatitis B surface antigen, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus, INR: International normalized ratio

Table 5: Case 3 investigations

Laboratory parameter	Day 1	Day 10
Hemoglobin (g/dL)	10.7	6.8
Total leukocyte count (/mm^3)	1800	2100
Differential leukocyte count (%)	41/48	43/49
Platelets (/mm^3)	43,000	30,000
Creatinine (mg/dL)	0.4	
Bilirubin (mg/dL)	0.9	4
AST/ALT/ALP	31/26/124	145/91/176
INR	1.1	1.4
S. Na/K (mEq/L)	134/3.6	
HIV/HbsAg/Anti-HCV	NR/NR/NR	

ALP: Alkaline phosphatase, ALT: Alanine transaminase, AST: Aspartate aminotransferase, HbsAg: Hepatitis B surface antigen, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus, INR: International normalized ratio

Table 6: Case 4 investigations

Laboratory parameter	Day 1	Day 7
Hemoglobin (g/dL)	6.2	5.8
Total leukocyte count (/mm^3)	2300	2100
Differential leukocyte count (%)	49/38	45/41
Platelets (/mm^3)	65,000	59,000
Creatinine (mg/dL)	1.1	
Bilirubin (mg/dL)	1	2.8
AST/ALT/ALP	78/95/141	212/123/205
INR	1.1	1.3
S. Na/K (mEq/L)	133/3.5	
HIV/HbsAg/Anti-HCV	NR/NR/NR	

ALP: Alkaline phosphatase, ALT: Alanine transaminase, AST: Aspartate aminotransferase, HbsAg: Hepatitis B surface antigen, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus, INR: International normalized ratio

chloroquine+primaquine. Even after completing the course, he remained febrile (up to 103°F); on the 4th day, he had an episode of epistaxis, prompting a complete blood count suggestive of anemia, leukopenia, and thrombocytopenia, following which he was referred to our hospital (Table 5). In the OPD, he presented with a fever. Pallor was present. The liver was palpable and it had a span of 16 cm span and the spleen was palpated 9 cm below the left costal margin. He was started on injectable antibiotics and artesunate. In spite of a full course of anti-malarial treatment, the fever persisted. Urine and blood cultures were sterile.

A rapid card test (testing rK39 antigen) and *Leishmania* antibody test were carried out that came to be positive. He was started on appropriate therapy for kala-azar, but his total leukocyte count (TLC) and platelets remained low (Table 5). Henceforth, bone marrow examination revealed a hemophagocytic picture with many macrophages showing engulfed platelets, leukocytes, and RBCs. S. ferritin was 4257 ng/mL.

He was then started on an injection of dexamethasone. After 5 days, his hemoglobin (Hb), TLC, and platelets began to rise.

A diagnosis of secondary HLH due to malaria and kala-azar was made and the patient was followed up over the next 8 weeks, and steroids were gradually tapered off. The patient remained asymptomatic.

CASE 4

A 44-year-old male presented with chief complaints of fever which was moderate-to-high grade for the past 2 weeks associated with leg pains, headache, and decreased appetite. The patient had an episode of generalized tonic-clonic seizure. There were no other associated complaints with fever. The patient was referred to our hospital with the diagnosis of pancytopenia with splenomegaly with a seizure episode (Table 6). In the emergency, the patient presented with a fever, and pallor was present. Examination revealed hepatomegaly as well as splenomegaly. The liver was firm and spanned 17 cm; the spleen was palpable 11 cm below the left costal margin. These were corroborated by ultrasonography.

His Widal test was highly positive. Dengue and chikungunya serology were also negative. Serum cholesterol was 230 mg/dL, serum triglyceride level was 860 mg/dL, and ESR was 45 mm/h. Blood cultures turned out to be negative but his IgM antibody test to *Salmonella* typhi was positive. Antibiotic therapy was started but the patient did not show any response. S. ferritin turned out to be 1256 ng/mL and bone marrow examination was suggestive of hemophagocytosis. Hence, a diagnosis of secondary HLH due to enteric fever was made and the patient showed remission after being adequately treated with steroids.

The clinical profile, laboratory investigations, treatment provided and outcome of the four cases have been summarised in Table 7.

Table 7: Summary of investigations in the series of HLH patients

Patient characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Age/sex	30/M	57/M	31/M	44/M
Chief complaints	Fever, jaundice, and vomiting	Fever and Jaundice	Fever	Fever and Seizure
Hemoglobin (g/dL)	4.3	11.1	6.8	5.8
Total leukocyte count (/mm^3)	2440	3550	2100	2100
Differential leukocyte count (%N/L)	38/53	47/43	43/49	45/41
Platelets (/mm^3)	12,000	86,000	30,000	59,000
Bilirubin (mg/dL)	15.6	7.2	4	2.8
AST/ALT	353/76	144/111	145/91	212/123
INR	1.69	1.45	1.4	1.3
S. Ferritin (ng/mL)	7393	911	4257	1256
Tropical infection workup	*Leptospira*, Hepatitis E virus, and Herpes simplex virus 1+	Enteric fever+	Malaria and kala-azar+	Enteric fever+
Bone marrow showing Hemophagocytosis	+	+	+	+
Remission with steroids	Achieved	Achieved	Achieved	Achieved

ALT: Alanine transaminase, AST: Aspartate aminotransferase, HLH: Hemophagocytic lymphohistiocytosis

DISCUSSION

HLH is a disease of immune activation and excessive inflammation. The cause may be primary or secondary [3,4]. The pathophysiology behind this is excessive stimulation of Th1-mediated immune response due to uncontrolled activity of NK cells and cytotoxic T-lymphocytes, resulting in overproduction of tumor necrosis factor-alpha, interleukin-1, 6, 10, and interferon-gamma, leading to "cytokine storm" which is responsible for symptoms such as fever, rash, and vascular leak. In primary HLH, the perforin-mediated negative feedback from cytotoxic T-lymphocytes is impaired [4,5].

Infective etiologies have been found to be the leading cause of secondary HLH in India [6-8]. Zoonotic infections such as leptospirosis and leishmaniasis are endemic in India and so are feco-orally transmitted infections such as hepatitis A/E and enteric fever. Malaria being the most common vector-borne parasitic infection in India accounts for more than three-fourths of cases reported from South-East Asia [9-12].

In literature, each of these individually has been found to be causative of HLH, but to come across the occurrence of a medley of concomitant infections such as in case 1 (HEV, *Leptospira*, and HSV-1) or the double trouble in case 2 (malaria and kala-azar) leading on to HLH is a rare entity, making these cases extremely unique.

The aim of management is to break the cycle of hyperinflammation by the use of immunosuppressive therapies. Infection-associated HLHs, such as intracellular infections including tuberculosis, leishmaniasis, or rickettsial disease, may respond to specific antimicrobial treatments. In adults who are clinically stable and are responding to treatment of the infectious trigger of HLH watchful wait is recommended. Etoposide- and dexamethasone-based therapy may be used in patients not responding to antimicrobial therapies and/or steroids [5,13-15].

All our patients responded to the treatment of the infectious trigger. Non-responders to the underlying disorder responded to dexamethasone therapy which was tapered later. We did not have to use immunosuppressants other than corticosteroids. Our takeaway is a thorough investigation of the underlying cause/causes and its treatment along with the use of steroids is the key to management.

CONCLUSION

Acquired HLH may pose a diagnostic challenge, as an infectious trigger. The detection of HLH is often delayed or even missed in adults and patients continue to receive treatment for non-resolving infections. To avoid this, we must keep a high clinical suspicion in such non-resolving infective cases with organomegaly and cytopenias [10-13]. Prompt workup and diagnosis are essential as delay may lead to rapid multi-organ deterioration. Early therapy with corticosteroids remains the mainstay of the treatment protocol, and the use of other immunosuppressive drugs such as cyclosporine and etoposide may be indicated depending on severity.

PATIENT CONSENT

Informed written consents of all the patients have been duly taken for publishing of this case series.

AUTHORS CONTRIBUTION

Dr. Saloni Khattar was involved with data collection and writing the manuscript whereas Dr. Ajay Chhabra provided the data of his series of diagnosed patients. Dr. Permeet Bagga was helpful in doing the histopathology and providing the images.

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