(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 6, Issue 3 , Page No: 101-107
May-June 2023

IJMSCR

Hemophagocytic Lymphohistiocytosis in a case of Enteric Fever

Mallikarjun Kalashetty, Manjunath S, Mahesha Padyana, Santhosh Subramanian
Department of Hematology, Department of Internal Medicine,
Department of Critical Care Medicine, Department of Hematology
Manipal Hospitals, Bengaluru, Karnataka, India, 560017

***Corresponding Author:**
Dr. Manjunath S. M
Department of Hematology, Department of Internal Medicine,
Department of Critical Care Medicine,
Manipal Hospitals, Bengaluru, Karnataka, India, 560017

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

HLH can be a rare complication of typhoid infection that can occur very early in the course of illness. We describe a case of a previously healthy young man presenting with fever, loose stools and weakness of limbs. After ruling out neuroinfection and demyelinating diseases, he was treated for dyselectrolytemia which was the cause for his weakness. Workup for worsening cytopenia even after starting correction for Vitamin B12 deficiency and raised inflammatory markers was suggestive of HLH. Blood culture showed growth of cephalosporin sensitive Salmonella Typhi. He responded to culture sensitive antibiotics and steroids. Furthermore, interestingly eosinopenia was noted in the case at the time of presentation until clinical recovery. Absolute eosinopenia could be a potential diagnostic clue and prognostic marker for HLH associated with typhoid infection, but requires validation through further studies.

Keywords: NIL

Introduction

Diagnosing tropical infections in the Indian subcontinent can be challenging due to overlap and variation in clinical presentations, and unreliable rapid test sensitivity and specificity. Associated immune dysregulation like MODS, Sepsis or Hemophagocytic lymphohistiocytosis (HLH) delays diagnosis and treatment of the underlying condition adding to the mortality and morbidity caused by these infections.

Hemophagocytic lymphohistiocytosis (HLH), an immune dysregulation syndrome, is usually associated with viral infections but can also be associated with bacterial and parasitic infections. (*1*) HLH as a rare complication of typhoid infection can be difficult to diagnose due to overlapping symptoms. There are few case reports about HLH secondary to Salmonella infections.

This case report describes a 19-year-old boy who presented with loose stools, fever, weakness of lower limb, and cytopenia. After extensive evaluation, he was finally diagnosed with Enteric fever with HLH disease, which was initially masqueraded by coexisting Vitamin B12 deficiency and a negative typhoid rapid test.

Case Report:

A 19-year-old boy, engineering student in Bengaluru was referred from an associate tertiary care hospital with suspicion of Hemophagocytic-lymphohistiocytosis.

He had been feeling unwell for the last 8-9 days, starting with a global headache, followed by foul smelling loose stools and associated symptoms of anorexia, fatigue, loss of appetite, and feverishness. Reduction in frequency of loose stools was followed by development of continuous high grade fever, associated with headache and myalgia but with no chills or rigor. On Day 9, he suddenly experienced weakness in both legs and imbalance while walking after taking a shower, for which he was taken to a nearby hospital. He had no complaints of back pain, neck stiffness, altered sensorium or involuntary limb movements. The patient had no history of skin rashes, bleeding symptoms, respiratory or cardiac symptoms, and had an unremarkable medical and family history. He had not traveled or received recent vaccinations, and followed a vegetarian diet, consuming food in a paid-guest room and hotel. He had no addictive habits or active sexual history.

He was evaluated in another hospital for fever, tachycardia, hypotension, and weakness in both lower limbs along with areflexia. MRI revealed a cytotoxic lesion in the corpus callosum. Initial lab reports showed leukocytopenia with thrombocytopenia, mild AKI with dyselectrolytemia (hyponatremia, hypokalemia and hypocalcemia), transaminitis and elevated inflammatory markers. He was started on hypokalemia correction and other supportive measures.

Dengue, Weil Felix, Leptospira serologies, Rapid tests for typhoid and malaria were negative, but IV Ceftriaxone and oral doxycycline were started while awaiting blood culture reports. Peripheral smear showed a normal picture except for macrocyte. Urine and stool tests were normal, while stool culture results were pending. USG showed thickening in ileum and caecum with mild adjacent fat stranding and enlarged mesenteric lymph nodes, but no organ enlargement. A nerve conduction study ruled out any demyelinating conditions.

On Day 10, the patient's condition worsened with increased inflammation markers and worsening cytopenia. Procalcitonin was positive. Vitamin B12 deficiency was discovered. Chest X-ray was normal. HIV serology, HBsAg, and anti-HCV antibodies were negative, as well as ANA by IF. D-dimer was elevated with low normal fibrinogen level. INR was slightly elevated.

However, the patient's condition did not improve and inflammatory markers increased, despite IV Vitamin B12 injections and antibiotics. CT revealed splenomegaly with rest of the features consistent with USG findings. Antibiotics were escalated to IV Meropenem and Vancomycin in view of sepsis with cytopenia, despite which his leucocyte and platelet counts continued to drop. Sepsis, TB and even HLH were considered for differential diagnosis. He was suspected to have HLH as triglyceride levels were elevated and hence was started on IV Steroids and referred to our hospital for further evaluation and management.

	Day 9	Day 10	Day 11	**Day 12**	Day 13	Day 14	Day 15	Day 16
WBC Count	3400	900→ 600	380→ 100	1070	1900→ 2470	2610	5970	7280
Differential count N/L/M/E/B	83/13/3/ 0/0	75/20/4 /0/0	54/29/ 15/1/0 → 66/26/7/ 0/0	75/17/ 7/0/0	64/23/1 3/0/0 → 72/20/7 /0/0	71/24/5 /0/0	68/22/1 0/0/0	63/24/1 2/0/0

Volume 6, Issue 3; May-June 2023; Page No 101-107

Hemoglobin	15.6	13	12.5	12.8	12.3→ 13.6	12.5	12.4	12.3
MCV	102	103	105→ 106	95	95	96	103	103
Platelet count	79000	46000	28200 → 16000	14000	23000 → 27000	33000	57000	97000
AEC	-	-	-	0	0→0	0	0	7
LDH	1502	1552	-	1541	-	-	-	-
Sodium	125	126	-	130	-	-	-	-
Potassium	2.8	3.8	3.8	3.8	-	-	-	-
Creatinine	1.21	-	-	-	0.53	-	-	-
CPK	1551	-	-	-	-	-	-	-
CRP	206	306	326	-	-	-	-	-
Total Bilirubin	1.61	1.31	1.46	-	-	-	-	-
AST	368	496	571	503	416	-	-	-

Volume 6, Issue 3; May-June 2023; Page No 101-107

ALT	155	165	160	148	-	-	-	-
Fibrinogen	-	217	-	188	-	-	-	-
INR	-	1.44	-	0.96	-	-	-	-
Ferritin	-	8795	-	19467	14032	-	-	-
Triglyceride	-	-	261	348	-	-	-	-

Upon admission to our hospital(Day 12), the patient was afebrile but still hypotensive. Clinically he had subcentimeter lymph nodes in the cervical area and hepatomegaly with mild ascites, but no splenomegaly. Power in the limbs was normal. Hemogram showed slight improvement in leukocyte count but platelet count continued to drop. Serum Ferritin, LDH, and Triglyceride levels were elevated and Serum Fibrinogen was reduced. Liver transaminases were still elevated but stable, and PT, aPTT, and INR were normal. Reticulocyte count was 1.7%. We could not test for soluble CD25 levels and NK cell activity due to limited laboratory resources. Even then, the patient fulfilled 5 out of 8 HLH-2004 criteria and HScore was 238 with 98-99% probability of HLH. He was started on IV Dexamethasone 8 mg twice daily for HLH disease and monitored in the ICU while receiving IV fluids, Meropenem, Vancomycin, Vitamin B12 and oral folic acid. Brucella IgM came negative.

A bone marrow study was conducted after stabilizing the patient and transfusing one unit of SDP as a precautionary measure. The bone marrow was hypocellular with normal hematopoiesis in three lineages. However, there were increased histiocytes, and some of them showed hemophagocytosis. The AFB and Gram stains were negative for bacteria. The Hscore was recalculated to be 240, again indicating a 98-99% probability of HLH. A provisional blood culture reported Salmonella Typhi was found to be sensitive to ceftriaxone. As a result, the patient's antibiotics were changed to IV Ceftriaxone 2g BD, and blood counts closely monitored.

On the day 13, he showed clinical improvement and his blood counts and ferritin levels improved as well. The bone marrow biopsy report showed increased histiocytes with features that suggested hemophagocytic lymphohistiocytosis. He was then transferred out of the ICU and continued on the same treatment regimen. The patient's blood counts continued to improve, and hence was discharged on the eighth day of hospitalization after receiving five days of IV steroids. He was advised to continue IV Ceftriaxone for a total of 14 days and Dexamethasone as per the HLH protocol, with plans to taper it off during follow up.

Discussion:

HLH is a severe and potentially fatal condition caused by dysregulated immune activation that results in tissue damage and organ dysfunction. Pathogenesis of HLH involves mutations that affect cytotoxic functions of Natural killer cells and cytotoxic T-Lymphocytes making them ineffective in eliminating activated macrophages. This results in excessive and persistent activation of macrophages producing cytokine storms. HLH can be triggered by viral, bacterial, and parasitic infections, as well as by genetic mutations and rheumatological conditions. HLH is usually a diagnosis in the pediatric age group usually triggered by viral infections like Epstein Barr Virus, Cytomegalovirus, Human Simplex Virus and many others. But age of onset may be late due to

Volume 6, Issue 3; May-June 2023; Page No 101-107

genetic mutations that cause partial defects in protein function and may even be diagnosed in elderly age groups

In India, tropical infections such as malaria, dengue, typhoid, tuberculosis, leishmaniasis, and brucellosis are endemic and can result in HLH. These infections have varied and overlapping clinical presentations making it difficult to differentiate in initial stages. Co-infection, super-infection, sepsis and dysregulated immune response like HLH make it further difficult in establishing a diagnosis and delays the start of specific treatments which adds to the mortality and morbidity caused by these infections. Typhoid fever, caused by Salmonella Typhi or Paratyphi, is a food or waterborne infection Typhoid associated HLH can be a rare extraintestinal complication and usually not seen very oftenly in clinical practice. (*2*).

Clinical presentation of typhoid is highly variable with the most prominent symptoms being prolonged fever and headache, and early signs including rash, coated tongue, and relative bradycardia during the peak of high fever. Later over a period, may develop hepatosplenomegaly, lymphadenopathy and abdominal tenderness. About 27% of hospitalized patients with typhoid can have complications and more so if presentation is late. Gastrointestinal bleed and intestinal perforations are well known complications, but usually occurs in the 3rd-4th week of illness. HLH could be a very early complication of typhoid as macrophage is involved in the early stages of its pathophysiology. Neurological complications include meningitis, guillain-barre syndrome, neuritis and neuropsychiatric symptoms. Uncommon complications DIC, HLH, endocarditis, myocarditis etc can be prevented by prompt diagnosis and treatment of the infection. (*3*)

Enteric fever diagnosis relies on isolating the bacteria from various bodily fluids, such as blood, bone marrow, rose spots, stool, and intestinal secretions. Blood culture has a sensitivity of only 60% and is less effective if the patient has had prior antimicrobial treatment or is in the first week of illness. Bone marrow culture has a sensitivity of over 80%, and its yield is not reduced by prior antibiotic therapy. If multiple fluids are cultured, the yield increases to over 90%. Serologic tests such as Widal can't differentiate between active infections from prior infection or vaccination, while other rapid serologic tests have higher accuracy but are limited by cost and availability. (*3*)

Cytopenia, including leucopenia, eosinopenia, thrombocytopenia, and anemia, is a common finding in enteric fever. These may be caused by myeloid maturation arrest, a decrease in precursor blasts, and increased phagocytic activity of histiocytes in the bone marrow. (*4*)(*5*)(*6*) Few studies suggest that absolute eosinopenia could be a potential clue for the diagnosis of enteric fever in the early phase of infection. Patients with both absolute eosinophil count <14/mm3 and total leucocyte count <8x109 /L had a 95.6% chance of being diagnosed with enteric fever. (*7*)(*8*)(*9*) Even in our case absolute eosinopenia can be noted from the time of presentation until the time of clinical recovery. Many of the features of Typhoid overlap with HLH too. There are no specific laboratory tests that diagnose enteric fever or differentiate it from HLH. So when a patient presents with features of HLH, absolute eosinopenia might be a potential clue of underlying typhoid infection. But it requires validation through further studies.

DIAGNOSIS: Most HLH patients exhibit hepatitis, resulting in elevated levels of transaminases, LDH, and bilirubin. Association is such that if liver dysfunction is absent, other diagnoses should be considered. Liver dysfunction in HLH can lead to hypertriglyceridemia, abnormal coagulation, and DIC. Hemophagocytosis is not specific to HLH and is not necessary for diagnosis as it only indicates excess macrophage activation. (*5*) HLH diagnosis is based on the criterias used in HLH-2004 trial(*10*).

HLH diagnosis is challenging and can mimic conditions like MODS, sepsis, encephalitis and even Typhoid. The presentation of HLH is similar to these conditions, with acute or subacute febrile illness and multiple organ involvement. Early recognition and treatment are crucial for better outcomes. Criterias used in major trials may not diagnose all cases with HLH. Hence a diagnostic score called “HScore” has been developed, which estimates the probability of HLH. Hscore ≥250 confers a 99% probability of HLH, whereas a score of ≤90 confers a <1% probability of HLH. (11).

Treatment: In stable patients who are less acutely ill, treating the underlying condition alone may be preferred to avoid potentially toxic HLH-specific therapy, except in cases of EBV where HLH-specific

Volume 6, Issue 3; May-June 2023; Page No 101-107

therapy may be necessary. Recovery rates of 60-70% are seen with treatment of the underlying infection alone in reactive hemophagocytic syndrome. HLH associated with bacterial infections typically have a better prognosis than those associated with viral infections. Patients with HLH and worsening organ function should receive HLH-specific treatment immediately. (*12*)(*13*)

The first HLH treatment protocol "HLH-94", developed in 1994, significantly improved mortality rates in HLH patients by using Etoposide and Dexamethasone for an 8-week induction therapy period. CNS manifestations are treated with weekly intrathecal methotrexate and dexamethasone. Patients recovering are weaned off therapy, while others continue therapy as a bridge to allogeneic hematopoietic stem cell transplantation (HSCT). The HLH-2004 protocol used cyclosporine during induction, but did not show significant benefit over the HLH-94 protocol. More than half of patients treated with the HLH-94 regimen achieve five-year survival, but mortality rates in HLH remain high.

A literature review of 15 case reports on HLH in typhoid, mostly affecting pediatric and young adult patients, found that fever with pancytopenia and hemophagocytosis in bone marrow were consistent features in all cases. While the majority of cases responded well to antibiotics therapy alone, dexamethasone was used in only two cases. (*14*) In a case report of a 4-year-old child with typhoid and HLH, clinical features and laboratory findings were similar to our case, including eosinopenia. That case was managed supportively with regular transfusions and did not receive HLH-directed therapies. Though the prognosis was good, the duration of hospitalization and requirements for repeated transfusions were relatively higher. (*15*)

A recently reported case by Reshmi KR et al in 2023 shares similarities with the our case, including bicytopenia, hyponatremia, hypokalemia, elevated transaminases, and CRP. The initial empirical therapy was also ceftriaxone and doxycycline. Hemophagocytosis too was observed in the bone marrow. In that case cytotoxic lesions of corpus callosum were also seen along with other features suggestive of meningitis, whereas it is possible that the observed corpus callosum lesions seen in our case may be due to dyselectrolytemia or the Salmonella infection itself. In their case, patient developed features of HLH following diagnosis and treatment of salmonella. In contrast, in our case, HLH was recognized before the diagnosis of typhoid. In either of the cases clinical improvement was noted only after addition of steroids. (*16*)

In our case, twice daily IV Ceftriaxone 2g was administered for typhoid infection, while twice daily IV Dexamethasone 8 mg was given as induction therapy for HLH, with plans to taper as per the HLH-94 protocol. Etoposide was not used due to hypocellularity in the bone marrow, and adequate clinical response was observed with steroids alone. Prophylactic Oral fluconazole 200 mg once daily and double-strength co-trimoxazole twice a week were also used for neutropenia and immunosuppression. The patient responded well to HLH-directed steroid therapy and appropriate antibiotics and was discharged within five days of treatment initiation. Early use of dexamethasone under antibiotic cover may reduce mortality and morbidity in cases of HLH associated with typhoid. Further studies are needed to determine the efficacy of HLH-directed therapy with steroids alone and the recommended duration of treatment for optimal response.

Conclusion:

Clinicians should be aware of the possibility of immune dysregulation such as HLH can complicate tropical infections. Early recognition of HLH with a high degree of suspicion and timely HLH-directed therapy with dexamethasone alone, can lead to significant improvements in clinical outcomes. Hence high degree of suspicion is required to identify HLH in these cases. In addition, simple clues such as eosinopenia in differential counts can aid in the suspicion and diagnosis of underlying conditions, highlighting the importance of keen observations in diagnosing these diverse conditions.

References:

1. Rouphael NG, Talati NJ, Vaughan C, Cunningham K, Moreira R, Gould C. Infections associated with haemophagocytic syndrome. Lancet Infect Dis. 2007 Dec;7(12):814-22.
2. Singh ZN, Rakheja D, Yadav TP, Shome DK. Infection-associated haemophagocytosis: the tropical spectrum. Clin Lab Haematol. 2005;27:312-315

Volume 6, Issue 3; May-June 2023; Page No 101-107

3. David A. Pegues, Samuel I. Miller. Salmonellosis. Harrison's Principles of Internal Medicine. 21st Edition; 1291-1298
4. Serefhanoglu K, Kaya E, Sevinc A, Aydogdu I, Kuku I, Ersoy Y. Isolated thrombocytopenia: the presenting finding of typhoid fever. Clin Lab Haematol 2003; 25:63 5.
5. George N, Sethi P, Nischal N, Kumar A, Siripurapu G, Wig N, Vyas S. A Catastrophic Presentation of Enteric Fever with Secondary Hemophagocytic Lymphohistiocytosis. J Assoc Physicians India. 2018 Dec;66(12):11-12
6. Sood R, Roy S, Kaushik P. Typhoid fever with severe pancytopenia. Postgrad Med J 1997; 73:41 2.
7. Khosla SN, Anand A, Singh U, Khosla A. Haematological profile in typhoid fever. Trop Doct. 1995 Oct;25(4):156-8.
8. Ishaq U, Malik J, Asif M, Zaib H, Haider I, Zahid T, Abdul Sattar R, Ikram U. Eosinopenia in Patients With Typhoid Fever: A Case-Control Study. Cureus. 2020 Sep 10;12(9):e10359.
9. Swati Kapoor, Rajeev Upreti, Monica Mahajan, Abhaya Indrayan, Dinesh Srivastava. Absolute eosinopenia as a surrogate marker for enteric fever. In: 9th Edition of International Conference on Preventive Medicine & Public Health.; July 16-17; 2018 London, UK
10. Paul La Rosée, AnnaCarin Horne, Melissa Hines, Tatiana von Bahr Greenwood, Rafal Machowicz, Nancy Berliner et.al . Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019; 133 (23): 2465–2477
11. Debaugnies F, Mahadeb B, Ferster A, Meuleman N, Rozen L, Demulder A, et al. Performances of the H-Score for Diagnosis of Hemophagocytic Lymphohistiocytosis in Adult and Pediatric Patients. Am J Clin Pathol 2016; 145:862 70
12. Fisman DN. Hemophagocytic syndromes and infection. Emerg Infect Dis. 2000 Nov-Dec;6(6):601-8.
13. Arora, Navneet & Singla, Neeraj & Jain, Aleena & Sharma, Prashant & Sharma, Navneet. (2021). Secondary haemophagocytic lymphohistiocytosis (HLH) triggered by Salmonella typhi. Postgraduate Medical Journal. 98
14. Sánchez-Moreno P, Olbrich P, Falcón-Neyra L, Lucena JM, Aznar J, Neth O. Typhoid fever causing haemophagocytic lymphohistiocytosis in a non-endemic country - first case report and review of the current literature. Enferm Infecc Microbiol Clin (Engl Ed). 2019 Feb;37(2):112-116
15. Abbas A, Raza M, Majid A, Khalid Y, Bin Waqar SH. Infection-associated Hemophagocytic Lymphohistiocytosis: An Unusual Clinical Masquerader. Cureus. 2018 Apr 12;10(4):e2472
16. KR, Reshmi et al. An Uncommon Presentation of Typhoid Fever - HLH. BMH Medical Journal - p. 9-13, oct. 2022.

Volume 6, Issue 3; May-June 2023; Page No 101-107