

## CLINICAL PROFILE OF SECONDARY HEMOPHAGOCYtic LYMPHOHISTIOCYTOSIS (HLH) - A CASE SERIES

Ajmal N.M<sup>1</sup>, Arshad Muneerudeen<sup>2</sup>, Renny Issac<sup>3</sup>, Muraly C.P<sup>4</sup>

<sup>1</sup>Junior Resident, Department of General Medicine, Govt. Medical College, Thrissur, Kerala, India

<sup>2</sup>Lecturer, Department of General Medicine, Govt. Medical College, Thrissur, Kerala, India

<sup>3</sup>Associate Professor, Department of General Medicine, Govt. Medical College, Thrissur, Kerala, India

<sup>4</sup>Associate Professor, Department of Pulmonary Medicine, Govt. Medical College, Thrissur, Kerala, India

Received : 22/06/2023  
Received in revised form : 27/07/2023  
Accepted : 10/08/2023

**Keywords:**

HLH: Hemophagocytic Lymphohistiocytosis. MAS: Macrophage Activation Syndrome, CRP: C reactive protein, ARDS: Acute Respiratory Distress Syndrome.

Corresponding Author:

**Dr. Muraly C.P,**  
Email: muralycp@gmail.com

DOI: 10.47009/jamp.2023.5.4.386

Source of Support: Nil,  
Conflict of Interest: None declared

*Int J Acad Med Pharm*  
2023; 5 (4); 1930-1935



### Abstract

Hemophagocytic Lymphohistiocytosis (HLH) is an uncommon, life-threatening hyper inflammatory syndrome, caused by severe cytokinemia, due to an excessively stimulated but ineffective immune process. The presenting features of HLH are non-specific, mimicking many diseases, and therefore its early recognition remains a challenge. It requires a high index of suspicion and detailed analysis of clinical and laboratory findings to arrive at a diagnosis. The objective of this study is to study various causes and clinical profile of a series of Hemophagocytic Lymphohistiocytosis (HLH) cases.

## INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a severe hyper inflammatory syndrome resulting from a dysregulated immune response due to various triggers.<sup>[1]</sup> It is driven by excessive activation of cytotoxic T-lymphocytes, natural killer T-cells and macrophages with subsequent cytokine storm and multi-organ dysfunction.<sup>[2]</sup>

HLH is usually triggered by infection. Familial forms result from genetic defects in natural killer cells and cytotoxic T-cells, affecting perforin and intracellular vesicles. HLH is often under-diagnosed or missed, which contributes to its high morbidity and mortality. Early recognition is hence crucial. Current available treatment options include immunosuppression, immune modulation, chemotherapy, and biological response modification, followed by hematopoietic stem-cell transplant (bone marrow transplant). A number of recent studies have contributed to the understanding of HLH pathophysiology, leading to alternate treatment regimens; however, much work remains to raise awareness and improve the outcomes.<sup>[3]</sup> HLH can be rapidly progressive and potentially fatal if left untreated. A high level of suspicion for HLH is required in patients presenting with splenomegaly, an increase in liver enzymes, elevation of inflammatory markers such as serum ferritin and cytopenia. This case series contains presents 8 cases of HLH.

## CASE SERIES

### Case 1

A 17-year-old girl presented with high-grade fever (>103-degree Fahrenheit) associated with chills, more towards evening, for three weeks duration and swelling over the right side of the neck. She complained of sore throat during the initial few days from the onset of fever. Later she noticed painful movements of her fingers and her right knee. The joint involvement was non-migratory and pain used to improve with activity. She also reported recent weight loss of 4 kg in the past one month. There was history of macular rash during fever spikes over the abdomen and trunk, sparing the face which used to disappear when the fever subsided. On examination she had pallor, bilateral cervical lymphadenopathy and tachycardia. There was no tonsillar enlargement or hepatomegaly. Clinically there was mild splenomegaly. Other system examination was found to be normal. Later on, she developed oral ulcers and one episode of epistaxis. We considered possible diagnoses of lymphoma, tuberculosis, infectious mononucleosis and Still's disease. Investigations showed pancytopenia with severe neutropenia and elevated transaminases. Peripheral smear report showed a normocytic normochromic blood picture, leukopenia and thrombocytopenia with reactive lymphocytes. Paul-Bunnell test was negative. FNAC of the lymph node showed reactive changes. ANA-IF and Rheumatoid factor were negative and blood

and urine cultures were sterile. Abdominal ultrasound and chest x-ray were normal. Viral markers (HIV, HBV, and HCV) and tuberculosis work up were negative.

She had continued fever spikes and progressively worsening neutropenia and liver enzyme levels. In view of the deteriorating general condition, we considered the possibility of underlying macrophage activation. She had elevated serum ferritin (1510 ng/L), triglycerides (287 mg/dL), LDH (4808 IU/L) and D-Dimer (0.5).

Bone marrow biopsy reported trilineage hematopoiesis with scattered histiocytes. Lymph node excision biopsy showed lymphocyte depletion with proliferation of histiocytes and hemophagocytosis. This picture was suggestive of Hemophagocytic Lympho Histiocytosis (HLH). At this point we considered the possibility of a viral infection triggering HLH. Serological tests for Her IgM and IgG Viral capsular Antigen for Epstein Bar Virus were positive.

She was diagnosed to have EBV infection causing secondary HLH and was started on Inj. Dexamethasone 8mg iv 12<sup>th</sup> hourly. After 2 days from starting treatment, her blood counts improved, fever subsided, and transaminase levels decreased. Later on, she was put on oral prednisolone 40mg once daily. During follow up visit after 2 weeks, her hemogram and LFT improved and she was symptomatically better.

#### **Case 2**

60 year old male presented with high grade fever with chills and rigor, abdominal pain, significant weight loss, ankle edema, breathlessness dyspepsia early satiety for 9months. Clinically he was anemic, with hepato splenomegaly. The differential diagnoses of Malaria, blood dyscrasias, parasitic infestations, and myelofibrosis were considered. Investigations showed anemia, elevated serum ferritin, and triglycerides. The ultrasonologic evidence of huge splenomegaly rose suspicion of Myelofibrosis and leishmaniasis. The bone marrow biopsy was inconclusive with no evidence of myelofibrosis. A Liver biopsy was done in view of elevated liver enzymes and alkaline phosphatase. Liver biopsy reported showed LD bodies, RK-39 antigen test was positive and leishmaniasis (*Leishmania donovani* zymodeme MON-37) was confirmed with peripheral blood and bone marrow aspirate DNA sequencing. A repeat bone marrow was done which showed numerous intracellular LD bodies consistent with visceral leishmaniasis. Hemophagocytosis and histiocytes collection was also seen. Patient was managed with Liposomal Amphotericin B 10 mg/kg single dose infusion over 2 hours, multivitamins, Iron supplements, human albumin, a balanced diet, good hydration, Calcium and Vitamin D. IV dexamethasone 6mg 8<sup>th</sup> hourly was given for 5 days (followed by oral steroids in tapering dose) in view of secondary HLH. Fever subsided in 8 days and the patient gained weight in 2months. The spleen size

reduced to 2 cm in 1 month. Counts normalised in 45 days but hypoalbuminemia persisted.

On third month of follow up, patient again started to lose weight, recurrent episodes of fever, pedal oedema, exertional dyspnea, anorexia and early satiety reappeared. He had features of treatment failure as the repeat PCR test for leishmaniasis came out as positive. The proposed treatment options for treatment failure viz. pentavalent antimony, miltefosine and paramomycin were not available. Hence we administered high dose liposomal Amphotericin B 5mg/kg/day for 5 days. He was also treated with broad spectrum antibiotics and other supportive measures including mechanical ventilation but eventually he succumbed to his illness.

#### **Case 3**

70 year old lady presented with high grade fever with rigor and chills for 3 days. She had severe anorexia and fatigue. She was pale, icterus with tachycardia and tachypnea who desaturated on room air corrected by nasal oxygen. Fine crackles appreciated over lung bases. A polymorpho nuclear leukocytosis, elevated ESR, Hemolytic jaundice with peripheral smear evidence of hemolysis. LDH was highly elevated and the direct Coomb's test was negative. Chest X ray showed bilateral consolidations. In view of the atypical symptoms with pneumonia, IgG and IgM Mycoplasma antibody also were done and found to be negative. She had an initial relief from fever for 2 days on Inj. Piperacillin Tazobactam and Azithromycin. However fever reappeared in 2 days with clinical and hematological deterioration. Serum ferritin and triglycerides were markedly elevated. A bone marrow study revealed histiocytic proliferation with hemophagocytosis consistent with HLH. Methyl prednisolone pulse of 1 gm was given for 5 days and she started to show improvement both clinically as well as hematologically. On the fifth day, the patient developed dyspnea with fall in oxygen saturation. A repeat chest X-ray showed diffuse bilateral non-homogenous opacities predominantly in lower zones. She was tested positive for COVID-19. Patient was intubated and mechanically ventilated in view of respiratory failure but eventually she succumbed to her illness.

#### **Case 4**

15 year old male presented with high grade, associated with rigor and chills fever and abdominal pain. It was associated with severe abdominal pain which initially was diffuse and later became localized to right iliac fossa. It was also associated with multiple episodes of vomiting and watery diarrhea. On examination of the abdomen features of acute appendicitis were elicited. Ultrasound and CT abdomen showed thickening and inflammation of appendix, cecum and terminal ileum. Blood investigations showed severe leucopenia with neutropenia and reactive lymphocytosis and a high CRP. Serum amylase and lipase were normal. The peripheral smear which showed pancytopenia with severe neutropenia and thrombocytopenia along with

low reticulocyte count. A provisional diagnosis of neutropenic enterocolitis with sepsis induced bone marrow suppression was made.

He was treated with IV broad spectrum antibiotics and supportive measures. In view of pancytopenia, we did a bone marrow examination which revealed marked megakaryocytic proliferation and fibrosis with atypical cells and many histiocytes with occasional cells having hemophagocytosis. (To consider hematological malignancy, possibly AML M7 with secondary HLH). S.Ferritin (1695) and triglycerides(288) were elevated. In view of HLH, he was given iv Immunoglobulin at a dose of 1g/kg/day for 2 days and in view of severe neutropenia he was given 3 doses of Granulocyte Macrophage Colony stimulating factor injection. The counts improved and patient became asymptomatic with treatment. A repeat bone marrow biopsy was negative for any hematological malignancy.

In view of suspicion of AML M7. Bone marrow study was repeated which showed trilineage hematopoiesis with areas of stromal edema and fibrosis and occasional megakaryocytes (Flow cytometry: 0.2% myeloblast, 10.9% monocytes, 9.3% mature T lymphoid cells, 2.3% B lymphoid cells, 1.6% NK cells). Since the repeat bone marrow was not suggestive of any hematological malignancy, he was kept under follow up. 1 month later, he had intermittent episodes of fever, bilateral cervical lymphadenopathy. Excision biopsy from the lymph node showed evidence of Non-Hodgkins lymphoma (positive for CD10 and TDT).

#### **Case 5**

50 year old female, vegetarian, with no known comorbidities presented to surgery OPD with abdominal pain of 1 week duration. It was dull aching type of pain in the right upper quadrant. There was no jaundice. She had a low grade fever which started along with abdominal pain, lasted for 2 days and subsided without any medications. There was no alteration in bowel habits or gastrointestinal bleed. On examination, she was afebrile, had knuckle hyperpigmentation with glossitis and there was tenderness in the epigastrium and right upper quadrant. On investigation, Amylase and Lipase was normal. X-ray abdomen erect showed no evidence of bowel obstruction. USG abdomen showed a normal pancreas and bowel but the gallbladder was minimally distended with a minimal pericholecystic fluid but no calculi. Blood counts showed a bicytopenia ( Hb- 8.8g/dL, platelet count- 14000/mm<sup>3</sup>). A peripheral smear showed marked anisopoikilocytosis with micro, normo and macrocytes, occasional hypersegmented neutrophils and thrombocytopenia (Platelet count of 15000/mm<sup>3</sup>) suggestive of Vitamin B12 deficiency. She was treated with parenteral methylcobalamine and other supportive measures. She had bleeding from oral cavity while brushing her teeth and on examination we found wet purpura. The repeat platelet counts showed a further fall, which was not fitting with diagnosis of Vitamin B12 deficiency alone. In the

background of fever with thrombocytopenia and leucopenia, an IgM dengue was done which came out to be positive. 2 days later, she developed postural hypotension associated with pedal edema and periorbital edema. A working diagnosis of capillary leak syndrome secondary to dengue fever which was supported by the presence of vomiting, with worsening of the abdominal pain and abdominal distension. Chest x-ray showed bilateral pleural effusion. An ultrasound of the abdomen showed acalculous cholecystitis associated with peri cholecystic collection and moderate ascites. Blood counts were repeated to look for hemoconcentration due to capillary leak, but instead showed pancytopenia (Hb- 5.9 g/dL, WBC – 1800/mm<sup>3</sup>, platelet count- 8000/mm<sup>3</sup>). Subsequently, a bone marrow study was done which showed normoblastic and megaloblastic maturation in erythroid series and few scattered histiocytes, some showing ingested RBCs suggestive of HLH. Serum Ferritin was 1778 and serum triglyceride was 321, which supported the diagnosis. She was started on Methyl Prednisolone 1g IV. On the 3rd day, she desaturated .and a repeat chest x-ray showed bilateral lung infiltrates suggestive of ARDS. She was intubated and mechanically ventilated but she succumbed to her illness.

#### **Case 6**

38 year old male, mason by profession, smoker and alcoholic with high risk sexual behavior detected to have diabetes 8 years back and had moderate non proliferative diabetic retinopathy, presented with 8 months history of weight loss(20kg in 6 months) and loss of appetite along with recurrent episodes of fever with night sweats for 1 month. It was associated with cough with expectoration but no hemoptysis or breathlessness. He also noticed a painless swelling in his right axilla. On examination, he was emaciated, pale and had icterus with bilateral axillary lymphadenopathy. There was extensive oral candidiasis. The respiratory system examination showed coarse inspiratory crackles on right infra-clavicular area. Abdomen examination showed hepatosplenomegaly. Chest X ray showed right upper zone consolidation. Sputum AFB was negative but CB-NAAT for MTB was detected. HRCT thorax showed cystic bronchiectatic changes in the apical segment of right upper lobe. A lymph node excision biopsy was performed and showed granulomatous lymphadenitis with caseous necrosis suggestive of Tuberculosis. HIV ELISA was positive and HBsAg and Anti-HCV were negative. Blood investigations showed elevated liver enzymes and conjugated hyperbilirubinemia. Ultrasound abdomen showed hepatosplenomegaly and no evidence of any cholestasis, which was suggestive of a possible granulomatous hepatitis. Blood counts showed pancytopenia, which was thought to be due to tuberculosis infiltrating the marrow. A bone marrow study showed no evidence of tuberculous infiltration instead, showed the presence of hemophagocytosis with histiocytic proliferation. The ferritin (>40000)

and triglyceride (312) was done subsequently, which favoured HLH.

He was initiated on modified anti TB regimen (and HAART was planned after 2 weeks of ATT). In view of HLH with pancytopenia, patient was given high dose steroids(methylprednisolone). The patient went into respiratory failure after a bout of massive hemoptysis and succumbed to his illness despite mechanical ventilation and other supportive measures.

#### Case 7

14 year old male presented with high grade, intermittent fever with chills and loose stools for 1 week and non-productive cough for 3 days. There was no breathlessness, jaundice, abdominal pain, vomiting, myalgia, neurological deficits or joint pains. He enjoyed some street food while on his visit to north India. Other family members also had similar illness. On examination, the boy had multiple petechial spots over the chest, abdominal wall, thighs and legs which blanched on applying pressure. The routine blood investigations showed pancytopenia with disproportionately low ESR.

A provisional diagnosis of enteric fever was made and the patient was started empirically on IV ceftriaxone with other supportive measures. But fever and pancytopenia were persisting, which prompted us to send serum ferritin, triglycerides, blood culture and a bone marrow biopsy with culture. The serum triglyceride levels were 230 and serum ferritin was 39800. Suspecting a secondary HLH, patient was started on methylprednisolone pulse, following which he started showing clinical improvement. The Widal titre showed 1:400 for S. Typhi, blood and bone marrow cultures returned positive for S. Typhi sensitive to ceftriaxone. The bone marrow biopsy showed trilineage hematopoiesis with evidence of hemophagocytosis. The patient was continued on ceftriaxone IV for 14 days, oral Azithromycin for 5 days and methylprednisolone pulse for 5 days; then changed to oral steroids which were tapered, along with supportive care which resulted in resolution of fever and clinical improvement.

#### Case 8

65 year old male, manual laborer, was admitted with complaints of on and off fever, night sweats for the past 1 month associated with significant loss of weight and loss of appetite. He had Coronary Artery disease, type 2 Diabetes mellitus and Systemic Hypertension. He was a smoker and occasional

alcohol abuser. On examination, patient was febrile. Vitals were stable. He had pallor and hepatosplenomegaly. On investigations, there was pancytopenia with a high LDH (625). A peripheral smear was suggestive of microcytic hypochromic anemia with leucopenia and thrombocytopenia with a low reticulocyte count (0.6%). CECT abdomen was suggestive of hepatomegaly with a prominent portal vein and a splenomegaly with non-enhancing focal lesions in periphery and parenchyma suggestive of hematopoietic/lymphoid neoplasm (no para-aortic/mesenteric lymphadenopathy). Subsequently, a bone marrow study was done-Aspirate showed a trilineage hematopoiesis with histiocytic proliferation and hemophagocytosis; and the trephine biopsy showed infiltration from Non-Hodgkins lymphoma (tumor cells positive for CD-20). Further investigations showed a high ferritin (>1500) and hypertriglyceridemia. Patient was initiated on IV methyl prednisolone pulse for 5 days. The fever subsided and the pancytopenia improved and he was referred to radiation oncology for further treatment. An echocardiogram showed normal LV function. He was thus initiated on RCHOP-E regimen. The patient went into remission with chemotherapy and is currently under follow up.

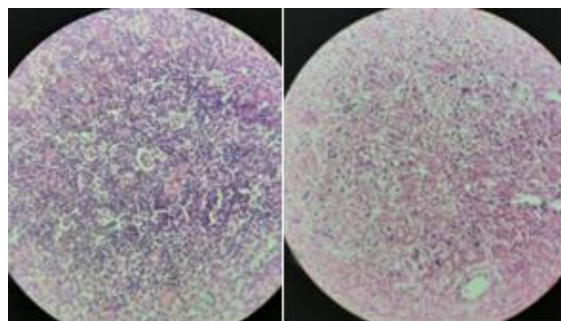


Figure 1: Lymph node biopsy showing histiocytes and hemophagocytosis (H&E stain)

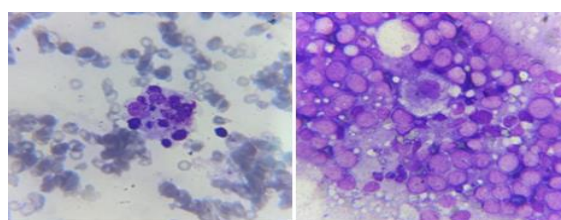


Figure 2: Bone marrow showing hemophagocytosis consistent with HLH

Table 1: Cytopenias, Serum Ferritin and Serum triglyceride levels in secondary causes of HLH

Cause of HLH	Cytopenias			Ferritin	Triglycerides	Treatment Given	Outcome
	Hb	TC	Platelet count				
IMN	7.7	700	84000	1510	187	Dexamethasone	Cured
Leishmaniasis	6.9	2000	91000	1354	335	Dexamethasone	Died
Mycoplasma	7.2	2000	13000	>2000	384	Methyl Prednisolone	Died
NHL	8.3	490	29000	1695	283	IV Ig	Cured
Dengue	5.9	1800	8000	1778	321	Methyl Prednisolone	Died
HIV+TB	7	560	48000	>40000	312	Not given	Died
Enteric fever	12	1700	34000	39800	230	Methyl Prednisolone	Cured
NHL	6.3	2100	22000	>1500	424	Methyl Prednisolone	Cured

**Table 2: Site of hemophagocytosis, the treatment given and mortality among secondary causes of HLH**

Cause of HLH	Site of Hemophagocytosis	Treatment given for HLH	Mortality
IMN	Lymph node	Dexamethasone	No
Leishmaniasis	Bone Marrow	Dexamethasone	Yes
Mycoplasma	Bone Marrow	Methylprednisolone	Yes
NHL	Bone Marrow	IVIg	No
Dengue	Bone Marrow	Methylprednisolone	Yes
HIV+TB	Bone Marrow	Not given	Yes
Enteric fever	Bone Marrow	Methylprednisolone	No
NHL	Bone Marrow	Methylprednisolone	No

## DISCUSSION

Hemophagocytic lymphohistiocytosis (HLH) covers a wide range of related diseases viz. HLH, autosomal recessive familial HLH (FHL), familial erythrophagocytic lymphohistiocytosis, viral-associated hemophagocytic syndrome,<sup>[4]</sup> and autoimmune-associated macrophage activation syndrome (MAS). These disorders are characterized by severe cytopenias due to uncontrolled hemophagocytosis. Other clinical symptoms and laboratory abnormalities result from disordered immune regulation and cytokine storm. The term primary HLH refers to a genetic abnormality causing the disorder,<sup>[4-6]</sup> whereas secondary HLH means that the disorder is secondary to underlying conditions such as infection, autoimmune/rheumatologic,<sup>[3]</sup> malignant, or metabolic conditions.

EBV and human immunodeficiency virus (HIV) were the most frequent infections causing HLH, while lymphoma was the most commonly associated malignancy.<sup>[6-10]</sup> MAS is seen in a variety of different rheumatic diseases in adults and children, but is most frequently reported in systemic juvenile idiopathic arthritis (sJIA) and its adult equivalent, adult-onset Still's disease.<sup>[11]</sup> In addition, a diverse range of drugs have been found to cause MAS, including biological therapies.<sup>[12,13]</sup>

The diagnosis of FHL or secondary HLH is based on a number of clinical signs and laboratory findings. Due to the relatively nonspecific nature of the clinical signs and symptoms, and significant overlap with other illnesses, diagnosis is challenging and often delayed. The diagnosis of HLH is established by the modified 2009 HLH diagnostic criteria and H-score.<sup>[14,15]</sup> Prior to the use of modern treatment options, death due to HLH was almost inevitable.<sup>[16]</sup> Briefly, treatment of HLH involves immune-suppressive and modulatory agents, biological response modifiers, treatment of the inciting illness if secondary, and subsequent stem-cell transplantation.<sup>[5]</sup>

EBV is the cause of heterophile antibody positive infectious mononucleosis (IMN), presenting as fever, sore throat, lymphadenopathy and atypical lymphocytosis and is also associated with some tumors including nasopharyngeal carcinoma and lymphomas.<sup>[17,18]</sup> Kala-azar (KA) also known as visceral leishmaniasis is a parasitic disease,<sup>[19,20]</sup> caused by *L.donovani*. HLH is rare in VL and can complicate the diagnosis of leishmaniasis. Bone marrow study is diagnostic in 78% of cases but is

often unyielding during the initial stages due to the pauci-microbial nature of the disease<sup>(21)</sup>. Liposomal AmB (L-AmB) has been the drug used in leishmaniasis.

A more thorough search of an underlying lymphoproliferative disorder is warranted if a patient presents with HLH and detectable EBV infection because early diagnosis and treatment of the underlying malignancy will have a significant effect on the disease outcome. It should be agreed upon that the approach of treating the cytokine storm initially, in some patients, may result in delay or missing the diagnosis of underlying lymphoma in HLH. In our patient, who had severe inflammatory symptoms, we believe that if we would not have initiated therapy, the patient would not have survived his HLH at initial presentation. However, underlying lymphoma should be ruled out using repeated testing and when recognized and the cytokine storm controlled, the underlying cause should be targeted

Dengue virus is the causative organism for dengue fever which belongs to the genus flavivirus within the Flaviviridae family.<sup>[22-24]</sup> Patients with severe dengue are also at risk of developing secondary HLH which would further contribute to the high mortality.<sup>[25,26]</sup> Viral infections are a common trigger of HLH but the exact mechanisms implicated in the pathogenesis of HLH remain unproven.

Haemophagocytic Lymphohistiocytosis (HLH), during HIV infection is a rare complication with a grave prognosis.<sup>[27]</sup> The specificity of HLH among HIV-infected patients is that its etiology is mostly infectious and mostly due to the disseminated infection. Disseminated histoplasmosis and tuberculosis are two very common opportunistic infections of patients with advanced HIV disease.<sup>[28,29]</sup> With the worsening of immunodeficiency, dissemination of the pathogen causes a rapid and fatal progress in the absence of treatment.<sup>[30,31]</sup>

Typhoid fever remains an important etiology of fever in developing countries.<sup>[32]</sup> The natural course of Typhoid Fever can range from an uncomplicated febrile illness to life-threatening sepsis with multi organ dysfunction and HLH.<sup>[33,34]</sup>

### Observations

It is noteworthy that, out of 8 patients, 4 received inj. Methylprednisolone pulse therapy for HLH, of which 50% improved and 50% expired. Dexamethasone, on the other hand, was given to 2 patients resulting in improvement of one and mortality in the other. One patient who received IV Immunoglobulin showed a



favourable clinical outcome and one patient expired before receiving any immunosuppressive therapy.

## CONCLUSION

This case series highlights the fact that secondary HLH can occur in a multitude of clinical settings. The features of HLH might take time to evolve and initial bone marrow biopsies may not be suggestive, as was seen in case 2. A high index of suspicion is necessary to have a quick and accurate diagnosis and timely intervention; otherwise the disease can be fatal. Timely detection of this very fatal complication and prompt intervention is life-saving and we hope our case series would guide physicians in the future for early detection of this rare.

## REFERENCES

1. Birndt S, Schenk T, Heinevetter B, Brunkhorst FM, Maschmeyer G, Rothmann F et al. Hemophagocytic lymphohistiocytosis in adults: collaborative analysis of 137 cases of a nationwide German registry. *Journal of cancer research and clinical oncology*. 2020 Apr;146(4):1065-77.
2. Lehmborg K, Ehl S. Diagnostic evaluation of patients with suspected haemophagocytic lymphohistiocytosis. *British journal of haematology*. 2013 Feb;160(3):275-87.
3. George MR. Hemophagocytic lymphohistiocytosis: review of etiologies and management. *Journal of blood medicine*. 2014;5:69
4. Meazza Prina M, Martini F, Bracchi F, Di Mauro D, Fargnoli A, Motta M, Giussani C, Gobbin G, Taverna M, D'Alessio A. Hemophagocytic syndrome secondary to SARS-Cov-2 infection: a case report. *BMC Infectious Diseases*. 2021 Dec;21(1):1-5.
5. Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. *Blood, The Journal of the American Society of Hematology*. 2015 May 7; 125(19):2908-14.
6. Goudarzipour, K et al. "Epstein-barr virus-induced hemophagocytic lymphohistiocytosis." *International journal of hematology-oncology and stem cell research* vol. 7,1 (2013): 42-5.
7. Li J, Wang Q, Zheng W, Ma J, Zhang W, Wang W, Tian X. Hemophagocytic lymphohistiocytosis: clinical analysis of 103 adult patients. *Medicine*. 2014 Mar;93(2).
8. Davies SV, Dean JD, Wardrop CA, Jones JH. Epstein-Barr virus-associated haemophagocytic syndrome in a patient with juvenile chronic arthritis. *Br J Rheumatol*. 1994;33:495-7.
9. Heaton DC, Moller PW. Still's disease associated with Coxsackie infection and haemophagocytic syndrome. *Ann Rheum Dis*. 1985;44:341-4.
10. Me´nard F, Besson C, Rince´ P et al. Hodgkin lymphoma associated hemophagocytic syndrome: a disorder strongly correlated with Epstein-Barr virus. *Clin Infect Dis* 2008;47:5314.
11. Sawhney S, Woo P, Murray KJ. Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders. *Arch Dis Child*. 2001;85:421-6.
12. Ravelli A, Caria MC, Buratti S, Malattia C, Temporini F, Martini A. Methotrexate as a possible trigger of macrophage activation syndrome in systemic juvenile idiopathic arthritis. *J Rheumatol*. 2001;28:865-7.
13. Ramanan AV, Schneider R. Macrophage activation syndrome following initiation of etanercept in a child with systemic onset juvenile rheumatoid arthritis. *J Rheumatol*. 2003;30:401-3.
14. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. *European journal of pediatrics*. 2007 Feb;166(2):95-109.
15. Fardet, Laurence et al. "Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome." *Arthritis & rheumatology (Hoboken, N.J.)* vol. 66,9 (2014); 2613-20. doi:10.1002/art.38690.
16. Weitzman S. Approach to hemophagocytic syndromes. *Hematology 2010, the American Society of Hematology Education Program Book*. 2011 Dec 10;2011(1):178-83.
17. Pagano, J S. "Epstein-Barr virus: the first human tumor virus and its role in cancer." *Proceedings of the Association of American Physicians* vol. 111,6 (1999): 573-80. doi:10.1046/j.1525-1381.1999.t01-1-99220.x
18. Cohen, Jeffrey I. "Primary Immunodeficiencies Associated with EBV Disease." *Current topics in microbiology and immunology* vol. 390,Pt 1 (2015): 241-65. doi:10.1007/978-3-319-22822-8\_10.
19. Chandran P, Thavody J, Lilabi MP, Rao B, Nair MS, Shamin PR. Visceral Leishmaniasis in Kerala: An Emerging Disease. *National Journal of Community Medicine*. 2016 Aug 31;7(08):722-4.
20. Mortazavi H, Soori T, Khamesipour A, Khatami A, Vasheghani-Farahani A. Co-existence of cutaneous leishmaniasis with pleural effusion: a case report from Iran. *Acta Medica Iranica*. 2014:231-3.
21. Rajagopala S, Dutta U, Chandra KP, Bhatia P, Varma N, Kochhar R. Visceral leishmaniasis associated hemophagocytic lymphohistiocytosis—case report and systematic review. *Journal of Infection*. 2008 May 1;56(5):381-8.
22. Guzman MG, Halstead SB, Artsob H, Buchy P, Farrar J, Gubler DJ, Hunsperger E, Kroeger A, Margolis HS, Martínez E, Nathan MB. Dengue: a continuing global threat. *Nature reviews microbiology*. 2010 Dec;8(12):S7-16.
23. World Health Organization , Regional Office for the Eastern Mediterranean . Dengue and severe dengue. World Health Organization. Regional Office for the Eastern Mediterranean; 2014.
24. Suppiah J, Ching SM, Amin-Nordin S, Mat-Nor LA, Ahmad-Najimudin NA, Low GK, Abdul-Wahid MZ, Thayan R, Chee HY. Clinical manifestations of dengue in relation to dengue serotype and genotype in Malaysia: A retrospective observational study. *PLoS neglected tropical diseases*. 2018 Sep 18;12(9):e0006817.
25. Chang CY, Rajappan M, Zaid M, Ong EL. Dengue fever complicated by hemophagocytic lymphohistiocytosis: Report of 2 cases and bone marrow findings. *Clinical case reports*. 2020 Dec;8(12):3426-30.
26. Kan FK, Tan CC, von Bahr Greenwood T, Khalid KE, Supramaniam P, Hed Myrberg I, Tan LH, Henter JI. Dengue infection complicated by hemophagocytic lymphohistiocytosis: experiences from 180 patients with severe dengue. *Clinical Infectious Diseases*. 2020 May 23;70(11):2247-55.
27. Nguyen D, Nacher M, Epelboin L, Melzani A, Demar M, Blanchet D, Blaizot R, Drak Alsibai K, Abboud P, Djossou F, Couppié P. Hemophagocytic lymphohistiocytosis during HIV infection in Cayenne Hospital 2012–2015: First think histoplasmosis. *Frontiers in Cellular and Infection Microbiology*. 2020 Sep 24;10:574584.
28. Nacher M, Adenis A, Abboud P, Djossou F, Demar M, Epelboin L, Couppié P. HIV patients dying on anti-tuberculosis treatment: are undiagnosed infections still a problem in French Guiana?. *BMC Research Notes*. 2020 Dec;13(1):1-5.
29. Jones BE, Young SM, Antoniskis D, Davidson PT, Kramer F, Barnes PF. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. *American Journal of Respiratory and Critical Care Medicine*. 1993 Nov 1;148(5):1292-7.
30. Wheat LJ, Connolly-Stringfield PA, Baker RL, Curfman MF, Eads ME, Israel KS, Norris SA, Webb DH, Zeckel ML. Disseminated histoplasmosis in the acquired immune deficiency syndrome: clinical findings, diagnosis and treatment, and review of the literature. *Medicine*. 1990 Nov 1;69(6):361-74.
31. Jones BE, Young SM, Antoniskis D, Davidson PT, Kramer F, Barnes PF. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. *American Journal of Respiratory and Critical Care Medicine*. 1993 Nov 1;148(5):1292-7.
32. Buckle GC, Walker CL, Black RE. Typhoid fever and paratyphoid fever: systematic review to estimate global morbidity and mortality for 2010. *Journal of global health*. 2012 Jun;2(1).
33. Non LR, Patel R, Esmaeili A, Despotovic V. Case report: typhoid fever complicated by hemophagocytic lymphohistiocytosis and rhabdomyolysis. *The American Journal of Tropical Medicine and Hygiene*. 2015 Nov 11;93(5):1068.
34. Bhan MK, Bahl R, Bhatnagar S. Typhoid and paratyphoid fever. *The Lancet*. 2005 Aug 27;366(9487):749-62.