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Haemophagocytic Lymphohistiocytosis (HLH) in a case of Enteric Fever

Vineeta Pande[1], S. R. Agarkhedkar[2], Ayank Tandon[3]*, Aditya Agarwal[4]
Dr. D.Y. Patil Medical College, Hospital & Research Centre, Pimpri, Pune, Maharashtra, India.

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Abstract: HLH is an uncommon, life threatening clinical syndrome cause by a severe hyper inflammatory reaction triggered by an infectious agent. The characteristic symptoms of HLH are due to the persistent stimulation of lymphocytes and histiocytes, leading to hyper-cytokinemia. We report a case of HLH in enteric fever in a13 year old female presenting with fever, lymphadenopathy and pancytopenia due an infection caused by Salmonella.

Key words: Post infective fever, Organomegly, cytopenias, Hyper ferritinemias.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a somewhat rare yet an aggressive and life-threatening syndrome of excessive immune activation and tissue destruction. It involves a final common pathway of hypercytokinemia, which can result in end-organ damage and death. It generally affects in younger age, most since birth till 18 months of age, however, it is also children and adults at all ages. (Rosado and Kim, 2013; Janka and Lehmberg, 2013)[1, 2]. It covers a wide array of related diseases including HLH, autosomal recessive familial HLH (FHL), familial erythrophagocytic lymphohistiocytosis, viral-associated hemophagocytic syndrome, and autoimmune-associated macrophage activation syndrome (MAS)[3]. However, its generalized classification is based on the genetic and non-genetic etiology. When HLH occurs owing to an underlying genetic abnormality then it is called as primary HLH whereas secondary HLH indicates that the disorder is secondary to underlying conditions such as infection, autoimmune/ rheumatologic, malignant, or metabolic conditions. Infection is a common trigger both in those with a genetic predisposition and in cases involving other etiologies. Owing to its rare occurrence and aggressiveness often leading to poor outcome, the clinical course and treatment planning is often interesting. In this case report we discuss a case of HLH diagnosed and managed at our facility.

Case Report

A 13-year-old female child born of a non-consanguineous marriage presented to our facility with a history of fever, cold, abdominal pain and nausea for the last 15 days. Before attending our facility, the patient was diagnosed as typhoid and had a history of intravenous antibiotics. On history taking, patient was reported to have underwent tonsillectomy 4 months back. The patient's younger brother had a history of Duchenne muscular dystrophy (DMD), which is an X-linked genetic disorder.

On admission, patient's heart rate was 104 beats/min, respiratory rate 30/min, blood pressure 100/70 mmHg and oxygen saturation of 100%. The CRT was <3 sec. On examination patient was found to have pallor and cervical and inguinal lymphadenopathy >3 cm.

Abdomen was soft with diffuse tenderness present all over the abdomen, Liver palpable 6cm below Rt coastal margin. Liver span 12 cm. Spleen was 2cm palpable below left coastal margin. Respiratory, cardiovascular and central nervous system did not show any abnormality.

On the basis of history and clinical findings, the differential diagnosis was narrowed for enteric fever, malaria, acute viral hepatitis, acute gastritis and severe anemia.

Investigations

The patient was severely anemic (Hb 7.8 g/dl) with TLC of 2900/cumm, differential leukocyte count was N58L41M0E1 and platelet count indicating mild thrombocytopenia (PC 1.19 lakhs/cumm). Retic count was 1%.

On rapid test the patient was negative for malaria. S. bilirubin was 0.7 mg% and SGPT and SGOT were 113 IU/l and 460 IU/l respectively. Alkaline phosphatase level was 114 IU/l. Blood urea and creatinine were 15 mg% and 0.6 mg% respectively. S. protein, S. albumin and S. globulin levels were 5.7 gm%, 2.8 gm% and 3.1 gm% respectively. S. Na^+ and S. K^+ were 138 mmol/l and 4.1 mmol/l respectively. Widal test was Positive. Dengue IgG, IgM and NS1 were negative. HIV/HBsAg were also negative.

On blood culture Salmonella group of organisms were isolated which were sensitive to Cefoperazone + sulbactam, Moxifloxacin and Ciprofloxacin but resistant to Cefixime and Clavulanate respectively.

***Corresponding Author:**
Dr. Ayank Tandon,
Dr. D.Y. Patil Medical College,
Hospital & Research Centre,
Pimpri, Pune, Maharashtra, India.

The patient was non-responsive to I.V. Cefeperazone + sulbactam and other medications. Hence further investigations were carried out: S. ferritin was 3420 ng/ml, S. Triglyceride levels were 267 mg/dl and LDH was 843 IU/L.

Bone marrow aspiration was done and biopsy findings revealed predominant lymphocytes, few monocytes and occasional reticulum cells were seen thus probably indicating Hemophagocytosis ? Post infective.

The erythroid cells appeared mildly diminished show normoblastic erythropiesis with maturation arrest at the intermediate stage. The myeloid cells showed normal progressive maturation with about 2% blast. There was mild increase in the number of mature lymphocytes. Few reticulum cells were also seen. Thus bone marrow showed nonspecific changes. Finally, the diagnosis of secondary post-infective HLH was confirmed based on alternative diagnostic guidelines by the Histiocyte Society (Arico *et al.*, 1996; Henter *et al.*, 2007)[4, 5].

Management

The patient was initially managed by antibiotic therapy i.v. cefeperazone+ sulbactam was carried out for 7 days followed by 14 days' regimen of i.v. Piperacillin + Tazobactam and i.v. Vancomycin for 14 days.

During the patient stay in PICU patient pulses were feeble and she required NS boluses and inotropic support with i.v. dopamine. ECG & CPK levels was normal. Myocarditis was ruled out. One unit of blood transfusion and was given.

As the patient was not responding to treatment hence oral steroid was considered and patient was started with Tab Prednisolone and was given for 10 days. After starting steroid patient started responding to treatment and oral prednisolone was slowly tapered after 10 days. Patient required hospital stay of 1 month 4 days. The hematological course during treatment has been shown in Table 1 below:

Table 1: Hematological course during treatment

Date	Hb	TLC	DLC	Platelet	PBS
21/2	10.3	4, 400	N65L34E1M0	1, 42, 000	
26/2	7.8	2, 900	N55L41M0E1	1, 19, 000	
08/3	7.6	1600	N35L55M6E04	80, 000	NCHC
09/03	6.8	1200	N30L60E4M6	60, 000	NCHC
13/03	5.9	1, 000	N4L90M6E0	30, 000	NCNC
04/04	8.6	6, 600	N42L34E10M14	3.7 lakh	Normocytic hypochromic

Discussion

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 often delayed (George, 2014)[3]. In our case, there were certain limitations and basically we were limited only upto clinical signs and laboratory findings alone owing to paucity of advanced molecular diagnostic tests that can confirm the disease earlier. Owing to this the initial management was based on clinical features.

The official diagnosis of HLH is confirmed by fulfillment of one or both of the following criteria:

1. A molecular diagnosis consistent with HLH
2. Five out of the following nine diagnostic criteria for HLH:
   - Fever
   - Splenomegaly
   - Cytopenias (affecting two or more of three lineages in the peripheral blood)
   - Hypertriglyceridemia (>265mg/dl) and/or hypofibrinogenemia (<150mg/dl)
   - Hyper ferritinemia (>500mg/dl)
   - Hemophagocytosis in bone marrow/ spleen/ lymph nodes,
   - Low or absent natural killer (NK)-cell activity,
   - Elevated soluble CD25 (interleukin [IL]-2 receptor)

In our case, fever, splenomegaly and thrombocytopenia were the initial indicators and elevated ferritin, hypertriglyceridemia and hemophagocytosis in later course confirmed the diagnosis. The delay in diagnosis was probably owing to extreme rarity of disease, absence of risk factors like consanguinity and initial isolation of Salmonella species indicative of typhoid and thus guiding the course of management. Consanguinity has been reported to account for nearly 24% of HLH cases (Arico *et al.*, 1996)[4].

However, a prolonged non-responsive clinical profile and decrease in platelet count in the absence of any other plausible reason led us to explore further. In the absence of presence of other risk factors including genetic predisposition, and primarily indicated by a positive culture, the diagnosis was secondary post-infective HLH. HLH has since been associated with a variety of viral, bacterial, fungal, and parasitic infections, as well as collagen-vascular diseases (Morris *et al.*, 1985; Wong *et al.*, 1991; Onishi and Namluchi, 1994)[6, 7, 8].

All of the clinical and laboratory findings are readily linked to the pathophysiology of HLH. Fever is the result of inflammatory activity. Splenomegaly, cytopenias and hypertriglyceridemia may be the direct result of infiltration by lymphocytes and macrophages as well as direct hemophagocytosis. Elevated ferritin >10, 000 µg/L has been demonstrated to be 90% sensitive and 96% specific for HLH (George, 2014)[3].

The pathophysiology of infection-associated HLH following infection with nonviral pathogens may also be related to production of high levels of activating cytokines by host lymphocytes and monocytes. The relative frequency of association between infecting organisms (e.g., Mycobacterium tuberculosis, Salmonella Typhi, and Leishmania sp.) that trigger a TH1 immune response and reactive hemophagocytic syndromes might suggest that the syndromes result from a poorly regulated or inappropriate TH1 response to intracellular pathogens (Fisman, 2000)[9].

As these disorders are rare, there is no controlled clinical trials of therapies. For patients with reactive HLH associated with pathogens other than Epstein Barr Virus (EBV), supportive care and treatment of the underlying infection is associated with recovery in 60%-70% (Reiner and Spivak, 1988; Janaka *et al.*, 1998)[10, 11]. In our case, a combinatorial sequential antibiotic regimen probably acted as treatment to underlying infection. In this case, steroid therapy was considered to be appropriate as the patient was in pediatric age group where corticosteroids are the appropriate line of therapy. We followed the approach of adding the addition of a steroid for further suppression of hypercytokinemia and inflammation (Tothova and Berliner, 2014)[13].

In majority of patients with acquired HLH, the underlying mechanisms remain elusive which eventually hamper both diagnostic evaluation and therapeutic management of these patients. In this case, a continuous monitoring, logical diagnostic planning and timely intervention helped to avert the poor outcome.

References

1. Rosado FG, Kim AS. Hemophagocytic lymphohistiocytosis: an update on diagnosis and pathogenesis. Am J Clin Pathol. Jun; 139, 6, (2013): 713-27.
2. Janka GE, Lehmberg K. Hemophagocytic lymphohistiocytosis: pathogenesis and treatment. Hematology Am Soc Hematol Educ Program., 2013: 605-11.
3. George MR. Hemophagocytic lymphohistiocytosis: review of etiologies and management. Journal of Blood Medicine. 5 (2014): 69-86.
4. Arico M, Janka G, Fischer A, *et al.,* Hemophagocytic lymphohistiocytosis. Report of 122 children from the International Registry. FHL Study Group of the Histiocyte Society. Leukemia 10, 2(1996): 197–203.
5. Henter JI, Horne A, Arico M, *et al.,* HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 48, 2, (2007): 124–131.
6. Morris JA, Adamson AR, Holt PJ, Davson J. Still's disease and the virus-associated haemophagocytic syndrome. Ann Rheumatol Dis: 44 (1985): 349-53.
7. Wong KF, Hui PK, Chan JK, Chan YW, Ha SY. The acute lupus hemophagocytic syndrome. Ann Intern Med, 114 (1991): 387-90.
8. Onishi R, Namiuchi S. Hemophagocytic syndrome in a patient with rheumatoid arthritis. Intern Med, 33 (1994): 607-11.
9. Fisman DN. Hemophagocytic Syndromes and Infection. Emerging Infectious Disease, 6, 6, (2000): 601-608.
10. Reiner A, Spivak J. Hemophagocytic histiocytosis: a report of 23 new patients and a review of the literature. Medicine, 67 (1988): 369-88.
11. Janka G, Imashuku S, Elinder G, Schneider M, Henter JI. Infection- and malignancy-associated hemophagocytic syndromes. Secondary hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am, 12 (1998): 435-44.
12. Tothova Z, Berliner N. Hemophagocytic syndrome and critical illness: new insights into diagnosis and management. J Intensive Care Med. Oct; 30, 7 (2015): 401-12.

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