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Hemophagocytic Lymphohistiocytosis Secondary to Dengue: A Case Report

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ABSTRACT

The autoimmune condition known as hemophagocytic lymphohistiocytosis (HLH) is typified by the reactive hyperactivity of histiocytes and cytotoxic T cells, which causes hypertyrosinemia damage to cells and organ systems, ultimately resulting in multiorgan failure. Although there is growing evidence linking the dengue virus to secondary HLH with significant mortality, Epstein-Barr virus (EBV) is more frequently linked to this condition. It has a serious prognosis when linked to dengue infection and is correlated with the severity of the illness. Moreover, it is frequently misinterpreted as sepsis due to its overlap with dengue sepsis. We present a case of a 1-year-old male patient who had a dengue infection and further developed HLH with pulmonary infiltrates. The patient was admitted with symptoms of fever, nausea and vomiting. The physical examination was significant for Hepatomegaly. Viral serology was positive for Dengue NS1 antigen. Upon further investigation, the patient had hyperferritinemia, hypertriglyceridemia, transaminitis of hemophagocytosis which are typical indicators of HLH. Treatment was given in the form of antibiotics as the secondary bacterial infections along with other supportive measures. The patient responded positively to the line of management. Dengue associated HLH diagnosis is challenging, but is very important as early diagnosis is associated with better outcomes.

Keywords: hemophagocytic lymphohistiocytosis, hyperferritinemia, Hepatomegaly, Dengue

INTRODUCTION

The hyper immunoinflammatory, hyperferritinemic disease known as hemophagocytic lymphohistiocytosis (HLH) is typified by the unchecked activation and growth of cytotoxic T cells and histiocytes, which release copious amounts of inflammatory cytokines.

Mutations in the genes that produce cytotoxic T cells and natural killer (NK) cells are the main cause of HLH. These are employed to eradicate pathogen-infected cells, such as those infected with the dengue virus or the Epstein-Barr virus (EBV) [1]. These mutations involve the genes STX11, SH2D1A, PRF1, UNC13D, and ITK [2–3]. Secondarily, it can be brought on by illnesses that harm the immune system, whether they are malignant or non-malignant. Acute lymphocytic leukaemia, acute myeloid leukaemia, B-cell lymphoma, T-cell lymphoma, and myelodysplastic syndrome are examples of malignant conditions. Juvenile idiopathic arthritis, juvenile Kawasaki illness, systemic lupus erythematosus (SLE), juvenile and adult-onset Still's disease, and rheumatoid arthritis (RA) are non-malignant conditions associated with HLH [4]. The most frequent cause of HLH with unfavourable prognoses is Epstein-Barr virus (EBV) [5].

Its pathogenesis is same whether it is an acquired or inherited HLH. Simplified, it is proposed that when the triggers are encountered, it results in an uncontrolled immunological response. NK cell cytotoxicity is HLH's defining characteristic. Granule-dependent cytotoxicity has been connected to familial HLH. Unchecked proliferation and an overabundance of cytokines from the immune response result from the incapacity to eradicate antigen-presenting cells and contaminated ones. These cells infiltrate the organs

and release additional cytokines, which results in the clinical manifestation of HLH. The fever is brought on by interleukin 1 (IL-1), IL-6, and tumour necrosis factor (TNF)-alpha. Cytopenia is the outcome of TNF-alpha and TNF-gamma suppressing haematopoiesis. Hyperfibrinolysis results from the release of ferritin and plasminogen activator by activated macrophages.

In 1994, the Histiocyte Society put forward the diagnostic standard. This is regarded as a definition of the criteria for the diagnosis of HLH and was updated in 2004 [6]. The diagnosis of HLH can be made based on either five or more of the following clinical findings: fever ≥ 38.5°C, splenomegaly, cytopenia, hypertriglyceridemia, hemophagocytosis in bone marrow, spleen, lymph nodes, or liver, low or absent NK cell activity, elevated CD25 (α-chain of SIL-2 receptor), ferritin > 500 µg/L, or confirmation of the molecular diagnosis, such as pathological mutations of PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A, or BIRC4 [7].

Due to its rarity, range of presentation, and non-specific findings, the diagnosis of HLH becomes very challenging. There is growing evidence that a severe dengue virus infection can also result in secondary HLH with unfavourable consequences. A 43% increase in mortality is possible. We report a case of dengue associated HLH that had a successful outcome following timely diagnosis and appropriate intervention.

CASE HISTORY

A 1 year old male child was admitted in paediatrics department with the chief complaints of fever, headache, nausea and vomiting. He was hemodynamically stable and the serological investigation confirmed a dengue infection. On the fifth day of fever he entered the critical phase of dengue infection and took symptomatic treatment for 4 days and the patient was discharged. Again the fever reappeared on 5th day and consulted near by clinic and took antipyretics and antihistamines. On 10th day Dengue IGM and NS1 was again positive and the child was taken to the hospital and managed with Iv fluids and antipyretics. Fever was persisting and the child was becoming lethargy and decreasing blood counts.

On examination, BP was 100/60 mmHg, Heart rate was 130 beats per minute, Respiratory rate was 36 breaths per minute and the oxygen saturation was 99%.The cardiovascular, respiratory, and the Central Nervous System was normal. The abdominal examination showed hepatosplenomegaly ,minimal fluid abdomen and oedematous pancreas and bilateral pleural effusion.

Laboratory investigations showed that

	Day 1	Day 2	Day 3	Day 4	Day 5
Hemoglobin (10-14 gm/dl)	7.3	7.6	8	8.7	10.1
Hematocrit (32-45%)	22	25	27	29	32
MCV(77-95 fl)	62.8				
MCH (26.5pg)	20.4				
MCHC (33.2%)	32.4				
RBC count (3.2-5.4)	3.1				
White cell count (6000-14000 per microlitre)	18100	15500	11900	10800	10200
Platelet count (1.5-4 lakh per microlitre)	1.4	1.6	1.7	2.1	2.4
ALT (20-60 U/L)	142	138	118	112	
AST (5-45 U/L)	398	333	226	179	
Creatinine (0.04- 0.45 mg/dl)	0.3				

LDH (120-300 mU/L)	1299	994	794	560	
Ferritin (4.6 – 204 ng/ml)				863.29	213.69
Triglyceride (60-165 mg/dl)	563	441	470	429	
INR (<1.5)		0.9			
CRP (0.8-11.2 mg/L)	78.5	38.5	10.8	4.1	
D Dimer (upto 250 ng/ml)	926	792	727	643	

The kidney function test was normal. LFT showed serum bilirubin, Alanine transaminase [ALT] 142 U/L ,and Aspartate aminotransferase[AST] 398U/L. Emperical antibiotics were initiated for fever. Blood culture and the urine culture didn't show any bacterial growth. On the 2ND day, the fever was persistent and the patient developed tachypneoa.SpO2 was 88% in room air. Supplemental oxygen was initiated with 2 liters of oxygen through a nasal cannula to maintain oxygen saturation of 95%.In the next 12hr,oxygen requirement increased to 8 liters to maintain saturation over 95%.A USG chest revealed a mild pleural effusion on both right and left side. Two dimensional echo shows mild pericardial effusion and the serum D dimer were elevated.

Antibiotics were upgraded upto IV Cefuroxime 350mg Q8H, Inj Amikacin 100mg OD, Syp Clarithromycin 2ml BD. Supportive treatment was continued [Inj pantop 10mg,A to Z drops 1mlOD,Inj ondansetron 10.8mg BD, Enterogermina 1 vial OD,Z and D drops 1ml OD].From the 2nd until the 7th day in hospital, the fever continued. Serial blood investigation were done.

On the day four, serum ferritin level were done which showed the marked elevation. The hemolysis workup was sent[Lactate Dehydrogenase [LDH], reticulocyte, count, indirect bilirubin and platelet a viral panel including dengue and malaria smear was also ordered. Blood smear showed leucopenia with an increase in lymphocytes, microcytic hypochromic, anaemia with neutrophilic leukocytosis, left shift mild thrombocytopenia. The haematology team was consulted and their impression was HLH for which a bone marrow biopsy was conducted. Bone marrow study showed the normocellular reactive marrow with evidence of macrophage activation of hemophagocytosis. A dengue serology on the day 6 of fever was positive for IgM antibodies by ELISA but negative for IgG antibodies establishing the diagnosis of primary dengue infection with secondary HLH.

Given that the patient was clinically stable and there was a triggering condition, we opted for supportive measures rather than HLH specific therapy. The patient was given 2 units of packed RBC for anaemia. He improved over the next few days, became afebrile and was discharged after 10 days in the hospital. At the time of discharge the patient was given a medication plan of Syp. Cefditoren Pivoxil 2.5 ml TID for 7 days for infection, Tonoferon 8 drop TID for 3 month for anaemia, cholecalciferol drop 1 ml OD for 2 weeks to boost immunity, Bascillus Clausi Spores suspension 1 vial OD for 1 week as a probiotic, Syp. Fourts B 3 ml OD for 1 month as a multivitamin. His blood counts and biochemical parameters had recovered to almost normal levels. In the follow-up after 2 weeks, all the haematological parameters were normal and the patient was doing well.

DISCUSSION

Hemophagocytic lymphohistiocytosis is an aggressive and rare disease. The Dengue virus is a member of the Flaviviridae family, specifically the genus Flavivirus. Four different serotypes exist. A dengue infection is caused by the virus. Shock syndrome, sepsis, and thrombocytopenia are among the side effects of dengue fever (DF).

Five criteria—fever, splenomegaly, bicytopenia, hypertriglyceridemia and hypofibrinogenemia, and hemophagocytosis—were used to diagnose HLH [7]. The Histiocyte Society added three more criteria in 2004: high levels of soluble interleukin-2 receptors, hyperferritinemia, and reduced or non-existent NK-cell function. For HLH to be diagnosed, five of these eight requirements must be met. Because they require transferring samples to specialized centers, the NK cell activity and soluble IL2 receptor quantitation assays are not used in ordinary clinical practice; as a result, their applicability in daily practice is limited. This patient was diagnosed with secondary HLH because they met five of the eight criteria: splenomegaly, bicytopenia (reduction in platelets and leucocytes), hyperferritinemia, and the presence of hemophagocytes in the bone marrow.

Two categories of HLH exist. Primary HLH is the first kind, indicating a history of hereditary illness. The second kind is called secondary HLH, and it can be caused by rheumatologic, infectious, neoplastic, or other secondary factors. On the other hand, primary HLH may also be triggered by the infection [8].

Infection-associated hemophagocytic syndrome (IAHS) is the primary cause of subsequent HLH cases. The most frequent cause is EBV. The pathophysiology of secondary HLH is also linked to CMV, parvovirus, herpes simplex virus (HSV), varicella-zoster virus (VZV), measles virus, human herpesvirus 8, H1N1 influenza virus, parechovirus, and HIV.

The most prevalent viral disease in humans that is spread by arthropods is dengue. Asymptomatic illness to dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) are among the clinical symptoms of dengue. There are four dengue viruses (DENV) known to be the cause. DENV1, DENV2, DENV3, and DENV4 are these. DENV1, DENV3, and DENV4 are the four dengue viruses that have been found to cause HLH. Dengue-associated HLH has also increased as a result of the growing number of dengue cases detected each year [8–9].

A study investigated dengue-associated HLH cases and described that infants were more affected and cases were related to higher morbidity (100% ICU admission and longer stay) with a mortality of 4.5% more than dengue patients. As expected in the cases of HLH, dengue-associated HLH also developed anemia, splenomegaly, hepatomegaly, along with elevated aminotransferases. Contrarily, neutropenia and thrombocytopenia weren't observed in dengue-associated HLH patients. This feature can be due to the clinical characteristics of dengue. It was also observed that morbidity was higher in dengue-related HLH as compared to dengue alone [10].

Another study conducted on 180 dengue patients concluded that high dengue-HLH mortality makes it a candidate for a short course of HLH-directed treatment in specific patients. Prednisolone has been linked with lesser derangement in leukocyte and AST levels [11]. Treatment of HLH with dexamethasone and etoposide has shown a significant reduction in mortality in EBV-infection-related HLH.

In a study from Puerto Rico, which studied dengue-HLH in children, etoposide again showed better results [10]. The exact mechanism of etoposide in hyper inflammation isn't well understood, but its involvement in the selective deletion of activated T-cells and reduction of inflammatory cytokines improves the conditions of HLH [12].

The aim of management of infection associated HLH is to treat the underlying infection that triggered it. Most cases of HLH also need to be treated upfront with standard protocols. Regarding treatment of dengue associated HLH, review of the existing literature showed that few cases have recovered spontaneously with supportive treatment only. To control the hyperinflammatory condition, methylprednisolone or dexamethasone pulse dosages have been utilized in the majority of cases. In rare instances, intravenous immunoglobulin G has been utilized either by itself or in combination with methylprednisolone or

dexamethasone. Raju et al. reported successful use of intravenous immunoglobulin G in nineteen children suffering from dengue related HLH [13]. Srichaikul et al.[14], Tan et al. [15] and Wan et al. [16] have reported treating three adult patients successfully with combination of intravenous immunoglobulin G and dexamethasone or methylprednisolone. Since the patient presented with a high procalcitonin level and X-ray indications of a chest infection, substantial doses of steroids were not explored in this case due to the accompanying pancreatitis and concurrent sepsis. After being promptly diagnosed with HLH (on day four of hospitalization and day seven of fever) and receiving targeted medication, our patient who had severe dengue with evidence of plasma leak recovered without incident.

The treatment of dengue induced HLH by antibiotics for the secondary bacterial infection seems to be associated with a favorable outcome as this case. Secondary HLH and severe sepsis, systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS) share clinical and laboratory inflammatory phenotypes and therefore it is important to distinguish these conditions as therapeutic options are radically different.

CONCLUSION

The immune system mediates hemophagocytic lymphohistiocytosis, an inflammatory response to viral infections, malignancies, and immunological disorders. Cytokine storms are brought on by HLH, and the bone marrow displays lymphohistiocytic response and macrophagic hemophagocytosis. Although EBV is the most common viral infection known to cause HLH, dengue-induced HLH is also commonly seen. Dengue fever and HLH are correlated, which indicates a dangerous sickness. Pulmonary involvement in HLH is possible but rare. A strong index of suspicion is required since dengue may be ignored due to the co-occurrence of septicemia. The HLH-2004 and HScore criteria are used to diagnose HLH. Treatment focuses on the primary pathology.

The patient's condition may be considerably improved by early intervention, disease detection, and the guidance of suitable medication. HLH should be considered in the differential diagnosis of children and adults with symptoms of persistent fever, hepatosplenomegaly, and cytopenia.

Reference

1. Giang HT, Banno K, Minh LH, et al. - Dengue hemophagocytic syndrome: a systematic review and meta-analysis on epidemiology, clinical signs, outcomes, and risk factors. Rev Med Virol. 2018;28:0. doi: 10.1002/rmv.2005
2. Horne A, Ramme KG, Rudd E, et al. Characterization of PRF1, STX11 and UNC13D genotype-phenotype correlations in familial hemophagocytic lymphohistiocytosis. Br J Haematol. 2008;143:75–83. doi: 10.1111/j.1365-2141.2008.07315.x.
3. Arico M, Imashuku S, Clementi R, et al.: Hemophagocytic lymphohistiocytosis due to germline mutations in SH2D1A, the X-linked lymphoproliferative disease gene. Blood. 2001;97:1131–1133. doi: 10.1182/blood.v97.4.1131.
4. Wysocki CA., Comparing hemophagocytic lymphohistiocytosis in pediatric and adult patients. Curr Opin Allergy Clin Immunol. 2017;17:405–413. doi: 10.1097/ACI.0000000000000405.
5. Goudarzipour K, Kajiyazdi M, Mahdaviyani A., Epstein-barr virus-induced hemophagocytic lymphohistiocytosis. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3913132/ Int J Hematol Oncol Stem Cell Res. 2013;7:42–45.

6. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL., How I treat hemophagocytic lymphohistiocytosis. Blood. 2011;118:4041–4052. doi: 10.1182/blood-2011-03-278127.
7. Henter JI, Horne A, Aricó M, et al. , HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48:124–131. doi: 10.1002/pbc.21039.
8. Ray U, Dutta S, Mondal S, Bandyopadhyay S., Severe dengue due to secondary hemophagocytic lymphohistiocytosis: a case study. IDCases. 2017;8:50–53. doi: 10.1016/j.idcr.2017.03.013.
9. Comprehensive guideline for prevention and control of dengue and dengue haemorrhagic fever. Revised and expanded edition. https://apps.who.int/iris/handle/10665/204894 2011
10. Ellis EM, Sharp TM, Pérez-Padilla J, et al., Incidence and risk factors for developing dengue-associated hemophagocytic lymphohistiocytosis in Puerto Rico, 2008-2013. PLoS Negl Trop Dis. 2016;10:0. doi: 10.1371/journal.pntd.0004939.
11. Kawaguchi H, Miyashita T, Herbst H, et al., Epstein-Barr virus-infected T lymphocytes in Epstein-Barr virus-associated hemophagocytic syndrome. J Clin Invest. 1993;92:1444–1450. doi: 10.1172/JCI116721.
12. Johnson TS, Terrell CE, Millen SH, Katz JD, Hildeman DA, Jordan MB., Etoposide selectively ablates activated T cells to control the immunoregulatory disorder hemophagocytic lymphohistiocytosis. J Immunol. 2014;192:84–91. doi: 10.4049/jimmunol.1302282.
13. Ujjwayini Ray, Soma Dutta, Susovan Mondal, Syamasis Bandyopadhyay, Severe dengue due to secondary hemophagocytic lymphohistiocytosis: A case study, IDCases,Volume 8,2017,Pages 50-53,ISSN 2214-2509,
14. T. Srichaikul, S. Punyagupta, T. Kanchanapoom, C. Chanokovat, K. Likittanasombat, A. Leelasiri, Hemophagocytic syndrome in Dengue hemorrhagic fever with severe multiorgan complications J Med Assoc Thai, 91 (1) (2008), pp. 104-109
15. L.H. Tan, L.C.S. Lum, S.F.S. Omar, F.K. Kan, Hemophagocytosis in dengue: comprehensive report of six cases, J Clin Virol, 55 (1) (2012), pp. 79-82
16. W.F. Wan Jamaludin, P. Periyasamy, W.R. Wan Mat, S.F. Abdul Wahid, Dengue infection associated hemophagocytic syndrome: therapeutic interventions and outcome, J Clin Virol, 69 (2015), pp. 91-95