JMSR
Journal of Medical and Scientific Research

CASE REPORT

Hemophagocytic lymphohistiocytosis: Uncommon systemic inflammatory clinical syndrome

Papa Rao N[1], Rama Krishna T[2,*], Narayana Babu K[3], Vedaswi Rao V[1], Bhanu Kiran C[1], Mayuri S[1], Shilpa[1], and Ujwal Teja Y[1]

[1] Department of Internal Medicine, Krishna Institute of Medical Sciences, Kondapur, Hyderabad-500084, Telangana, India
[2] Department of Clinical Pharmacology, Krishna Institute of Medical Sciences, Kondapur, Hyderabad-500084, Telangana, India
[3] Office of the medical superintendent, Krishna Institute of Medical Sciences, Kondapur, Hyderabad-500084, Telangana, India.

Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme inflammation. HLH can be challenging to diagnose because the initial symptoms may mimic common infections. People with HLH usually develop symptoms within the first months or years of life which may include fever, enlarged liver or spleen, cytopenia and neurological abnormalities. HLH can only be diagnosed with the proper blood tests. A sample of bone marrow may be obtained to look for hemophagocytosis. Treatment depends on a number of factors, including the severity of symptoms, onset of age, and the underlying cause of the condition. Patients are usually treated with steroids plus chemotherapy and / or an antibody therapy that destroys the T cells. Patients may receive other medications that suppress the immune system. Many patients must also have their immune systems replaced by means of a bone marrow transplant in order to be cured of HLH. We report the brief description of a case along with treatment algorithm.

Keywords: cytopenia; hemophagocytosis; hemophagocytic lymphohistiocytosis

***Corresponding author:** Dr. T. Rama Krishna, Clinical Pharmacologist, Krishna Institute of Medical Sciences, Kondapur (Village), Hyderabad-500084, Telangana, India. Mobile: +91-9866468046; Email: ramakrishna.te@kimshospitals.com

Received 03 August 2016; *Revised* 07 September 2016; *Accepted* 17 September 2016; *Published* 29 September 2016

Citation: Paparao N, Ramakrishna T, Narayanababu K, Vedaswirao V, Bhanukiran C, Mayuri S, Shilpa, Teja UY. Hemophagocytic lymphohistiocytosis: Uncommon systemic inflammatory clinical syndrome. J Med Sci Res. 2016; 4(4):177-180. DOI: http://dx.doi.org/10.17727/JMSR.2016/4-039

Introduction

Immune system becomes over activated and damages the patient's own tissues and organs in hemophagocytic lymphohistiocytosis (HLH). The first reported case of HLH was described in 1952 by Farquhar and Claireaux, who called the disease familial hemophagocytic reticulosis and described it as a rare familial disorder characterized by proliferation of histiocytes in solid organs and phagocytosis of blood cells. It is also known as hemophagocytic syndrome, characterized by an uncommon systemic inflammatory clinical syndrome associated with numerous conditions, such as neoplastic, infectious, autoimmune, or hereditary diseases [1]. The disease is seen in all ages and has no predilection for race or sex. HLH is caused by a defect in inflammatory signals that

results in uncontrolled hypercytokinemia, usually in a setting of congenital or acquired defective natural killer (NK)/T-cell function in the cytotoxic pathway [2].

HLH has been traditionally divided into a primary form, which typically manifests in children with documented genetic abnormalities of the cytotoxic function of NK cells and T cells, and a secondary form that tends to occur at older ages in the setting of an associated condition, such as infection and malignancy, without an identifiable genetic abnormality [3, 4]. Establishing a timely diagnosis of HLH is the critical challenge that physicians face. The symptoms of HLH are nonspecific; thus, the disease is easily under-recognized. The confirmation of a suspected HLH case is also difficult because of a lack of a gold standard confirmatory test [5].

The clinical presentation of HLH is different in neonates. Fever in this age group is commonly absent and should not advise the clinician from pursuing the diagnosis of HLH. Similarly, hypertriglyceridemia, although frequently seen in adults, has been reported in only 14% of neonates. By contrast, coagulopathy, hepatomegaly, and cytopenias should raise suspicion for HLH in this population [6, 7]. HLH constitutes a medical emergency at any age. Because of the nonspecific nature of the clinical presentation, this disease is often overlooked, although the patients may be in extremis [8].

Case presentation

A 55-year-old male presented with a 12 days history of acute febrile illness and inability to sit. His past medical history was remarkable and he was taking medications (antibiotics, IV fluids and antipyretics). He was a known patient of hypertension and diabetes since thirteen years. He is on medications with losartan+hydrochlorthiazide for hypertension and oral hypoglycemic agents for diabetes. He presented with a temperature of 101.7^{o} F, a heart rate of 182/min, his abdomen was soft and non-tender with hepatitis. His initial blood work consisited of a diminished platelet count, WBC and hemoglobin. A sample of bone marrow reveals hemophagocytosis. Based on clinical and laboratory findings, it was confirmed as hemophagocytic lymphohistiocytosis.

On admission, patient was febrile (101.4^{o} F) with a pulse of 132/min, BP 110/60 mm of Hg, heart rate 98/min with a bilateral pitting edema and jaundice. Rest of the examination findings were normal. Patient was started on inj. Sulbactum+ cefaperazone 1.5 gm iv bd, inj. pantoprazole 40 mg iv bd, inj. Paracetamol 650 mg p/o 6th hourly, inj. Multivitamin, inj. Plasmolyte-A, tab. clarithromycin 1 gm stat (loading dose) and continued as 500 mg bd (maintainance dose). Advised diabetic soft diet. Antibiotics were prescribed to control the infection, antipyretics are prescribed to reduce the fever and supportive treatment like electrolyte supplements was given. Patient complaints of chills and rigors with a pulse 98/min, BP 120/100 mm of Hg on day two. Respiratory examination reveals bilateral wheezing. Patient was started on inj. Avil iv stat, 25 % dextrose stat, advise GRBC 2nd hourly, inj. Hydrocortisone 200 mg iv stat, stat nebulization (duolin+budecart), O_2 inhalation, tab. Amlodipine 5 mg p/o stat. No fresh complaints on day three but lab reports reveals delayed LFT'S. Inj. Glutathione 20 mg stat 6th hourly was added, inj. Lasix 10 mg stat and tab. Doxycycline 100 mg p/o bd. Referred to pulmonologist because patient complains of shortness of breath and was advised inj. amikacin 500 mg iv stat 1st dose 8th hourly and 2nd dose 12th hourly. A meropenam 1 gm, inj. Fluvir 150 mg bd, tab. Udiliv 300 mg p/o tid and stop sulbactum+cefoperazone were added. Aldosterone 1 gm stat on day four was added and inj. Fluvir, inj. paracetamol, tab. Doxycycline are stopped on day five. Inj. Methyl prednisolone 1 gm stat is added to relieve from SOB on day six and same treatment was continued till day seven because of no fresh complains. On day eight, tab. Fluconazole 150 mg od was added. Clarithromycin, meropenam were stopped and cholethemate sodium 2 milliunits, inj. Teicoplanin 400 mg, inj. Moxinic 1.2 gm iv bd were added on day nine. Cap. Ascoril-LS p/otid and folic acid+methylcobalamin was added on day ten. The patient's general condition was better and was discharged from the hospital. The symptoms of HLH are nonspecific so the disease is under-recognized. The above treatment helps to treat infections that are present, and/or prevent development of new infections.

Discussion

Common laboratory findings associated with HLH include cytopenias affecting at least 2 lineages in the peripheral blood, hypofibrinogenemia, strikingly elevated ferritin levels, and hypertriglyceridemia.

Hyperbilirubinemia with elevated transaminases and lactate dehydrogenase levels are also commonly seen and reflect liver dysfunction [9]. Histopathologic findings of HLH typically include a prominent and diffuse accumulation of lymphocytes and mature macrophages, which occasionally exhibit hemophagocytosis. Although classically seen in the bone marrow, these infiltrates also have been described in the spleen, lymph nodes, liver, skin, lungs, meninges, CSF, and, rarely, the subcutaneous tissue [10-13].

Based on these common clinical and laboratory findings, diagnostic criteria for HLH were proposed in 1991 and updated in 2004 to include NK-cell activity measured by the 51-Cr release assay, sCD25, and elevated ferritin. The diagnostic criteria include fever; splenomegaly; cytopenias affecting at least 2 of 3 lineages in the peripheral blood; hyperferritinemia greater than 10,000 µg/L; hypertriglyceridemia and/or hypofibrinogenemia; hemophagocytosis in the bone marrow, spleen, or lymph nodes; low or absent NK-cell activity determined by the 51-Cr release assay; and high levels of sCD25. Five of these 8 criteria are required for diagnosis. Mutation analysis should be requested for all cases of confirmed or suspected HLH, even when an associated infectious disease has already been identified. The demonstration of a characteristic genetic defect alone can be used to make the diagnosis of HLH in the appropriate clinical setting, without the need to fulfill 5 of the 8 diagnostic criteria. It should include the analysis of the known FHL (Familial forms of HLH) mutations (PRF1, UNC13D, STX11, and UNC18B) [14-16].

The therapy of HLH aims to suppress the exaggerated immune response through the use of immunosuppressive agents. Eight week induction therapy with corticosteroids, etoposide, and cyclosporine A as the backbone of HLH treatment. Corticosteroids are used to suppress the hypercytokinemia and cyclosporine A inhibits T-cell activation, and etoposide further blocks cell division and cell proliferation. Stem cell transplant (SCT) is indicated in selected cases [17, 18].

The prognosis of genetic HLH without treatment is poor, with a median survival of 1 to 2 months. The overall reported mortality for acquired HLH exceeds 50%. Among all the viruses associated with HLH, EBV carries the worst prognosis, with a reported mortality ranging from 25% to 100%. However, the addition of etoposide in the therapy regimen has yielded good results, especially if initiated within the first 4 weeks. Following a confirmed episode of HLH, it is important to rule out a genetic defect of FHL or primary immunodeficiency syndrome, which are associated with a high risk of recurrence and necessitate SCT for any prospect for a long-term cure [19-21].

Conclusion

Infections are common triggers in both genetic and acquired HLH. With better understanding of the pathogenesis of this disease subtype, newer and more specific testing may become available as well as novel targeted therapies. It is also critical to search for and treat underlying triggers of HLH.

Acknowledgements

Krishna Institute of Medical Sciences, Kondapur, Hyderabad-500084, Telangana, India.

Competing interests

The authors declare that they have no competing interests.

References

[1] Farquhar JW, Claireaux AE. Familial haemophagocytic reticulosis. Arch Dis Child. 1952; 27(136):519–525.

[2] Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. Annu Rev Med. 2012; 63:233–246.

[3] Larroche C, Scieux C, Honderlick P, Piette A, Morinet F, et al. Spontaneous resolution of hemophagocytic syndrome associated with acute parvovirus B19 infection and concomitant Epstein-Barr virus reactivation in an otherwise healthy adult. Eur J Clin Microbiol Infect Dis. 2002; 21(10):739–742.

[4] Buyse S, Teixeira L, Galicier L, Mariotte E, Lemiale V, et al. Critical care management of patients with hemophagocytic lymphohistiocytosis. Intensive Care Med. 2010; 36(10):1695–1702.

[5] Arico M, Janka G, Fischer A, Henter JI, Blanche S, et al. Hemophagocytic lymphohistiocytosis: report of 122 children from the International Registry. FHL Study Group of the Histiocyte Society. Leukemia. 1996; 10(2):197–203.

[6] Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007; 48(2):124–131.

[7] Suzuki N, Morimoto A, Ohga S, Kudo K, Ishida Y, et al. Characteristics of haemophagocytic lymphohistiocytosis in neonates: A nationwide survey in Japan. J Pediatr. 2009; 155(2):235-238.

[8] Freeman HR, Ramanan AV. Review of haemophagocytic lymphohistiocytosis. Arch Dis Child. 2011; 96(7):688–693.

[9] Allen CE, Yu X, Kozinetz CA, McClain KL. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2008; 50(6):1227–1235.

[10] Foucar K, Reichard K, Czuchlewski D. Bone Marrow Pathology. 3rd ed. Chicago, IL: American Society for Clinical Pathology. 2010.

[11] Hsi ED. Hematopathology: A volume in foundations in diagnostic pathology series. London, UK: Churchill Livingstone. 2007.

[12] Aronson IK, Worobec SM. Cytophagic histiocytic panniculitis and hemophagocytic lymphohistiocytosis: An overview. Dermatol Ther. 2010; 23(4):389–402.

[13] Henter JI, Elinder G, Ost A. Diagnostic guidelines for hemophagocytic lymphohistiocytosis. The FHL Study Group of the Histiocyte Society. Semin Oncol. 1991; 18(1):29–33.

[14] Janka GE, Schneider EM. Modern management of children with haemophagocytic lymphohistiocytosis. Br J Haematol. 2004; 124(1):4–14.

[15] Cetica V, Pende D, Griffiths GM, Aricò M. Molecular basis of familial hemophagocytic lymphohistiocytosis. Haematologica. 2010; 95(4):538–541.

[16] Horne A, Janka G, Maarten Egeler R, Gadner H, Imashuku S, et al. Haematopoietic stem cell transplantation in haemophagocytic lymphohistiocytosis. Br J Haematol. 2005; 129(5):622–630.

[17] Janka G, Imashuku S, Elinder G, Schneider M, Henter JI. Infection and malignancy associated hemophagocytic syndromes: Secondary hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am. 1998; 12(2):435–444.

[18] Imashuku S, Kuriyama K, Teramura T, Ishii E, Kinugawa N, et al. Requirement for etoposide in the treatment of Epstein-Barr virus associated hemophagocytic lymphohistiocytosis. J Clin Oncol. 2001; 19(10):2665–2673.