

The great masquerader: Hemophagocytic lymphohistiocytosis secondary to cytomegalovirus infection in an immunocompetent young man

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a rare, poorly recognized and underdiagnosed syndrome of excessive immune activation, which is rapidly fatal. HLH can occur as a familial or secondary disorder. Secondary HLH is most commonly associated with infections, malignancies, or autoimmune diseases. It primarily affects patients with a compromised immune system and rarely presents in immunocompetent individuals. Acute cytomegalovirus (CMV) associated HLH in the immunocompetent individual is extremely rare and only documented in five case reports till date. We, hereby, report a case of 18 years old young immunocompetent man who was diagnosed to have HLH secondary to CMV infection.

Keywords: Cytomegalovirus infection, hemophagocytic lymphohistiocytosis, immunocompetent

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon disorder with an incidence of 1.2 cases/million patients/year, with a shockingly high mortality rate.^[1] HLH is characterized by defective natural killer cell cytotoxicity, which results in inappropriately robust activation of macrophages and leads to engulfment of other blood cells. This manifests as a syndrome

of high fever, hepatosplenomegaly, lymphadenopathy, and cytopenias. HLH is frequently misdiagnosed for a septic syndrome, leading to a profound delay in diagnosis.^[2] HLH is divided into primary and secondary. Secondary HLH results from insults such as infection, malignancies, or autoimmune diseases. Secondary HLH is characteristically caused by an exogenous insult in an immunocompromised patient. Common causes are Epstein-Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), hepatitis A virus, herpes viridae, and bacterial, parasitic, and fungal etiologies.^[3] CMV-associated HLH has been reported in a variety of immunocompromised states such as solid organ transplantation and autoimmune disease.^[1] To our knowledge, CMV-associated HLH in an immunocompetent patient has been reported in the literature only on five other occasions.^[1,2,4-6] We hereby report a case of a

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young immunocompetent man presenting with pancytopenia and eventually diagnosed to have HLH secondary to CMV infection.

Case History

An 18-year-old young man presented with fever since 15 days and dry cough since 5 days. At presentation, the patient had pallor and hepatosplenomegaly on per abdomen examination. The patient's investigations showed hemoglobin of 9.5 gm%, total leucocyte count (TLC) of 1200/cumm (neutrophil-15%), and platelet count of 1.1 lac/cumm. Peripheral smear showed mild anisopoikilocytosis, mild hypochromia, normocytic to normochromic red blood cells and few microcytes. Patient's Serum Glutamic Oxaloacetic Transaminase (SGOT) and SGPT were elevated, i.e., 621 U/L and 246 U/L, respectively. Serum triglyceride levels were also elevated (273 gm/dl). The patient was evaluated on lines of pancytopenia. Malaria serology, rk 39, dengue serology, and scrub typhus serology were negative. Hbs antigen, anti-hepatitis C virus (HCV) and HIV were negative. Rheumatoid factor and antinuclear antibody were negative. Blood culture and urine cultures were sterile. During the stay in hospital, the patient also complained of diminution of vision. The fundus examination showed grossly defined hemorrhages. Bone marrow aspiration showed suppressed erythroid series, which was normoblastic in nature. Myeloid series showed normal maturation. Megakaryocytes were adequate. There was an increase in the number of macrophages that showed hemophagocytosis. There was no abnormal cell, granuloma, or parasite. The patient's serum ferritin was elevated (59013 ng/ml). Contrast-enhanced computed tomography (CECT) chest and abdomen showed hepatosplenomegaly with mild ascitis [Figure 1]. It also showed multiple centrilobular nodules with surrounding ground-glass opacities in bilateral lung fields and necrotic mediastinal lymphadenopathy [Figure 2]. The patient was diagnosed as HLH according to diagnostic guidelines for HLH -2004 [Table 1].^[7]

The patient was treated with a broad spectrum antibiotic for febrile neutropenia. The patient was treated with Inj Etoposide

and Inj dexa. Patient's CMV polymerase chain reaction (PCR) came out to be positive (1.1 *100 copies/ml) and he was started on antiviral (Inj gancyclovir). The patient was given blood transfusions. The patient did not respond and he subsequently developed type 1 respiratory failure because of the development of ARDS. Eventually, the patient succumbed to the disease and expired.

Discussion

HLH represents a syndrome of cytokine dysregulation and severe inflammatory response. It is one of the only several diseases featuring a markedly elevated ferritin level in addition to adult-onset Still's disease and lymphoma. Also, many conditions can lead to the clinical picture of HLH, including malignancies, infections (viral, bacterial or parasitic), and rheumatoid disorders.

In primary HLH, 80% of these cases are present in the first year of life. Examples of genetic conditions associated with

Table 1: Revised diagnostic guidelines for HLH^[7]

<p>The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled</p> <p>(1) A molecular diagnosis consistent with HLH</p>
<p>2) Diagnostic criteria for HLH fulfilled (five out of the eight criteria below)</p> <p>(A) Initial diagnostic criteria (to be evaluated in all patients with HLH)</p> <p>Fever</p> <p>Splenomegaly</p> <p>Cytopenias (affecting 2 of 3 lineages in the peripheral blood):</p> <p>Hemoglobin <90 g/L (in infants <4 weeks: hemoglobin <100 g/L)</p> <p>Platelets <100 10⁹/L</p> <p>Neutrophils <1.0 10⁹/L</p> <p>Hypertriglyceridemia and/or hypofibrinogenemia: Fasting triglycerides 3.0 mmol/L (i.e., 265 mg/dl)</p> <p>Fibrinogen 1.5 g/L</p> <p>Hemophagocytosis in bone marrow or spleen or lymph nodes</p> <p>No evidence of malignancy</p> <p>(B) New diagnostic criteria</p> <p>Low or absent NK-cell activity (according to local laboratory reference)</p> <p>Ferritin 500 mg/L</p> <p>Soluble CD25 (i.e., soluble IL-2 receptor) 2,400 U/ml</p>



Figure 1: CECT abdomen of patient showing hepatosplenomegaly

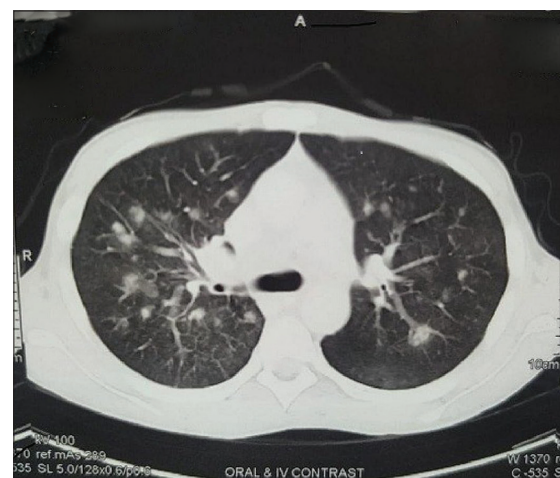


Figure 2: CECT chest of patient showing multiple centrilobular nodules with surrounding ground glass opacities in bilateral lung fields

primary HLH include Griscelli syndrome 2 (GS2) and Chediak Higashi disease (CHD).^[7] Secondary HLH arises due to an acquired precipitant. Both types have identical phenotypes characterized by inept NK cell/CD8+ T cell responses that lead to macrophage hyperactivation, proliferation, and infiltration into various organs.^[1]

The typical findings of HLH are fever, hepatosplenomegaly, and cytopenia. Other common findings include hypertriglyceridemia, coagulopathy, and hypofibrinogenemia, elevated levels of ferritin, raised serum transaminase, and neurological symptoms. Histopathological findings include widespread accumulation of lymphocytes and mature macrophages, sometimes hemophagocytosis especially affecting the spleen, lymph nodes, bone marrow, and liver.^[8]

H-score [Table 2] is used for determining the probability of having HLH.^[9,10] Our patient's H score was more than 250 which confers a 99% probability of HLH.

HLH is an established phenomenon among immunosuppressed and children. Cases occurring in immunocompetent adults are few. Even more rare is CMV-associated HLH in an immunocompetent patient [Table 3].^[2,4-6]

HLH can be rapidly progressive and potentially fatal if left untreated. A major breakthrough was the use of epipodophyllotoxin derivative etoposide (150 mg/m² per dose), in combination with steroids (IV/oral dexamethasone), which demonstrated induction of prolonged symptomatic resolution. The initial therapy covers the first 8 weeks of treatment [Figure 3]. There should be consideration of antiviral therapy in patients with ongoing viral infections, and intravenous immunoglobulin (IVIg) (0.5 g/kg IV) once every 4 weeks (during the initial and continuation therapy).

Patients who can be weaned off of dexamethasone and etoposide without recurrence, recover normal immune function, and have no identified HLH-associated gene defects may stop therapy after the 8-week induction. Hematopoietic stem cell

transplantation (HSCT) is generally recommended in patients with CNS involvement, recurrent/refractory disease, persistent NK cell dysfunction, or proven familial/genetic disease. Figure 4 shows a schematic treatment overview of the HLH-2004 protocol.^[7]

The mortality of secondary HLH and HLH in adults without treatment is high. Case series of adults treated with a variety of regimens report 30-day mortality of 20% to 44% and overall mortality of 50% to 75%.^[8] Therefore, early diagnosis and treatment are crucial. Physicians at primary care level should be sensitized about HLH, as simple clinical examination and hemogram tests can facilitate in the timely diagnosis of HLH.

Conclusions

HLH is a disorder that is usually present in immunocompromised patients but can be present in immunocompetent individuals

Table 2: Parameters included in H-Score and the number of points associated with each criterion for scoring^[9,10]

Variable	Points
Known underlying immunosuppression	0(no) or 18(yes)
Temperature(Celsius)	0(Less than 38.4) 33(38.4-39.4) 49(more than 39.4)
Organomegaly	0(no) 23(hepatomegaly or splenomegaly) 38(hepatomegaly and splenomegaly)
Number of cytopenia	0(1 lineage) 24(2 lineage) 34(3 lineages)
Ferritin(ng/ml)	0(less than 2000) 35(2000-6000) 50(more than 6000)
Triglycerides(mmol/l)	0(less than 1.5) 44(1.5-4) 64(more than 4)
Fibrinogen(g/l)	0(more than 2.5) 30(less than or equal to 2.5)
Serum aspartate aminotransferase(U/l)	0(less than 30) 9(more than or equal to 30)
Haemophagocytosis feature on bone marrow aspiration	0(no) 35(yes)

H score ≥250 confers a 99 percent probability of HLH, H score ≤90 confers a <1 percent probability of HLH

Table 3: Prior cases of CMV-associated HLH infection in immunocompetent host

Author	Age/Sex	Diagnosis of CMV	Diagnostic Criteria for HLH
Tsuda, Shirono, et al., 1996 ^[5]	21M	(+) CMV IgG and IgM	Fever, Splenomegaly, Cytopenia, Ferritin 1314, Positive BMB
Hot, et al., 2008 ^[4]	32F	(+) CMV IgM, CMV PCR 41,000	Fever, Splenomegaly, Cytopenia, Ferritin 88,300 ng/mL, Positive BMB
Yu-Tzu Tseng, et al., 2011 ^[2]	N/A	Generic Criteria	Reportedly met HLH2004 criteria and BMB+
Atim-Oltuk, et al., 2013 ^[1]	48F	CMV IgG/IgM (+), CMV PCR 19,000	Fever, Splenomegaly, Ferritin 40,000 ng/mL, Cytopenia, Hypertriglyceridemia
Bonnetaze et al. 2017 ^[3]	39-year-old morbidly obese female	positive CMV IgM, and CMV-DNA polymerase chain reaction (PCR)	Elevation of ferritin, persistent fever, splenomegaly, and new-onset hypertriglyceridemia

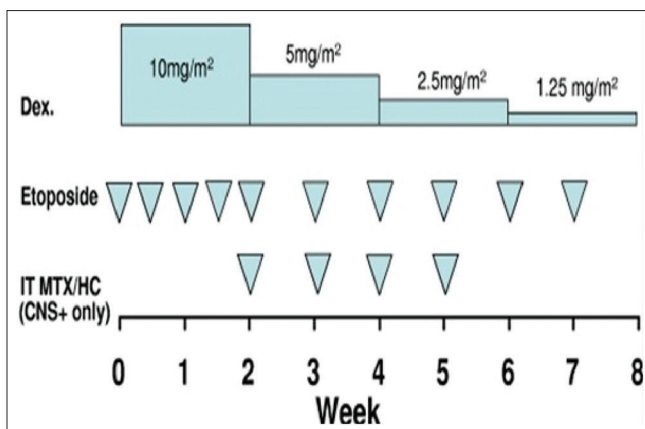


Figure 3: Induction therapy for treatment of HLH^[7] IT MTX/HC=Intrathecal methotrexate and hydrocortisone

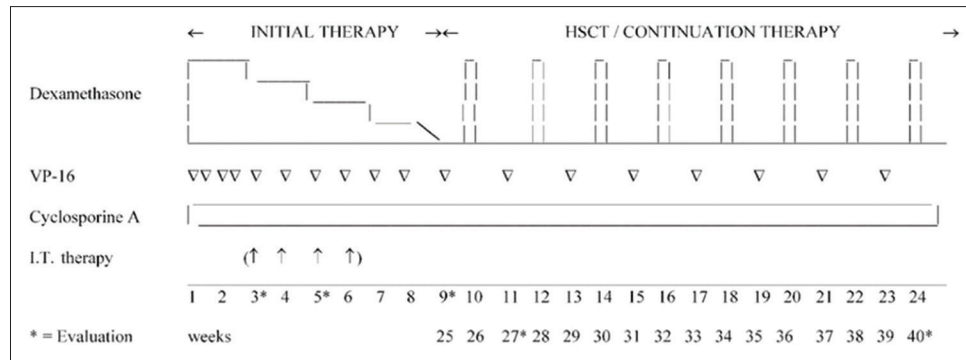


Figure 4: Schematic treatment overview of the HLH-2004 protocol.^[7] VP-16-etoposide, I.T. therapy- intrathecal methotrexate and corticosteroids, HSCT- hematopoietic stem cell transplantation

too. It is a great masquerader of other conditions because of its variable presentation and this often leads to delayed diagnosis. Prompt commencement of immunochemotherapy is essential for survival. Therapy is complicated by high risk of treatment-related morbidity and disease recurrence.

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Conflicts of interest

There are no conflicts of interest.

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