Hemophagocytic Lymphohistiocytosis Associated with Cytomegalovirus Infection in an Immunocompetent Infant: A Diagnostic and Therapeutic Challenge!

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Abstract Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal syndrome that results from inappropriate activation of the immune system. Many viral agents are known to trigger HLH but cytomegalovirus (CMV) associated HLH is rarely described. We report a case of CMV related HLH in a 3½ month old immunocompetent male infant who presented with fever, respiratory distress and hepatosplenomegaly. He had fulminant sepsis like course in the hospital as he continued to have hectic fever spikes, progressive pneumonia, increasing hepatosplenomegaly and multiple episodes of generalized convulsions. Investigations revealed bicytopenia, biochemical hepatitis, hyperferritinemia and hypofibrinogenemia. CMV IgM serology was reactive in both infant and mother. Diagnosis of CMV-HLH was made as per HLH 2004 diagnostic protocol. Infant was successfully treated with intravenous ganciclovir along with dexamethasone and etoposide.

Keywords Cytomegalovirus · Hemophagocytic lymphohistiocytosis · Immunocompetent · Infant

Introduction

Hemophagocytic lymphohistiocytosis (HLH) may develop as a result of strong immunological activation of immune

system. It includes two forms: primary (*familial or inherited*) and *secondary* HLH. Mutations in the genes encoding for perforin (*PRF1*), *UNC13D*, *Munc18/2*, syntaxin 11 (*STX-11*), syntaxin binding protein 2, (*STXBP2*) were identified in association with familial HLH (FHL) [1–3]. Secondary HLH (sHLH) was seen in association with viral (most frequent cause), bacterial, fungal, or parasitic infections, malignancy or rheumatoid disorder [1–4]. Viral infections, especially Epstein–Barr virus (EBV) may precipitate sHLH as well as FHL [2–4]. Herein, we describe a rare case of HLH associated with cytomegalovirus infection in an immunocompetent infant.

Case

A previously healthy 3½ month old male infant presented with high grade fever, cough for 3 days and breathlessness a day before admission. He was born of full-term normal vaginal delivery with birth weight 2.7 kg to a G1P1A0 mother non-reactive for HIV, VDRL, and HBSAg. There was no history of consanguineous marriage. The infant was exclusively breast fed. Examination revealed heart rate of 140/min, respiratory rate-60/min with chest retraction, normal blood pressure, prolonged CRT (4 s), pallor, hypoxia, bilateral crepitations and wheezing in the chest, and hepatosplenomegaly (a firm liver 4 cm and spleen 2 cm below costal margins).

Investigations were as follows—hemoglobin (Hb) 6.8 g/dL, total leukocyte count (TLC) 6,900 cells/cumm (31 % neutrophils, 63 % lymphocytes) and platelets 4,50,000/mm³. Chest radiograph showed opacity in the right middle zone. Patient was treated with intravenous cefotaxime, amikacin, and dopamine.

Since there was no satisfactory clinical response, repeat hemogram and a chest X-ray was ordered on day 3, which revealed bicytopenia (Hb 5.9 g/dL and TLC 2,600 cells/cumm)

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Table 1 Summary of laboratory investigations of the patient

CBC	Day 1	Day 3	Day 5	Day 8	Day 14	Day 18	Day 22	Day 28
Hb (g/dL)	6.8	5.9	8.6	8.1	8.6	6.3	8.2	8.6
TLC (per cumm)	6,900	2,600	2,400	4,300	2,600	1,000	6,000	7,000
Neutrophils	31	32	35	26	38	30	44	43
Lymphocytes	63	64	60	70	56	64	52	54
ANC	2,139	832	840	1,118	988	300	2,650	3,010
Platelets (per cumm)	4,50,000	2,50,000	2,10,000	1,50,000	1,50,000	1,20,000	1,50,000	6,80,000
Total bilirubin (mg/dL)			2.1					
ALT (IU/L)			90					
AST (IU/L)			71					
Serum CMV IgM, reactive ≥ 1				3.19 Reactive				
PT (s)					18			
PTT (s)					28			
Ferritin (ng/mL)						3,151		
Fibrinogen (mg/dL)						56		
Fasting triglyceride (mg/dL)						123		
Sr. sodium (meq/L)		137			133		136	

Hb hemoglobin, *TLC* total leukocyte count, *ANC* absolute neutrophil count, *ALT* alanine transaminase, *AST* aspartate transaminase, *PT* prothrombin time, *PTT* partial thromboplastin time

and progressive pneumonia on chest radiograph for which ampicillin and cloxacillin combination was added. He was transfused with packed red cells. Total bilirubin was 2.1 mg% (direct 1.2 mg%), AST 71 IU/L and ALT 90 IU/L. On day 7, the infant had 2 episodes generalized tonic–clonic convulsions which were terminated with phenobarbitone. Cerebrospinal fluid study could not be done as the patient was hemodynamically unstable. Blood culture, urine culture and Koch's work-up of the infant was negative. Considering drug resistant septicemia, antibiotics were changed to Meropenem and Linezolid.

In view of pneumonia, hepatosplenomegaly, convulsions, bicytopenia and biochemical hepatitis, serum CMV IgM was sent which came reactive. Also, positive urinary *CMV DNA Qualitative PCR* confirmed CMV infection in the infant. Brain ultrasound and ophthalmic examination were normal. Immunoglobulin analysis of the infant was normal (IgG 6.8 g/L, IgA 0.661 g/L, IgM 1.59 g/L). Mother's serum CMV IgM was also reactive. The infant was started on injection Ganciclovir (5 mg/kg/day BD). Day 11 onward, intermittent involuntary head nodding and clonic movements in right upper arm (epilepsia partialis continua) were noted which were controlled on antiepileptics. MRI brain done after the patient stabilized was normal.

Fever continued to persist. Fungal culture, repeat blood and urine culture were sterile. Peripheral smear for malaria was negative. Meanwhile he was treated with fluconazole and chloroquine for unremitting fever. Because of refractory fever, bicytopenia and ongoing hepatosplenomegaly, bone marrow and work up for HLH was planned which

revealed elevated ferritin (3151 ng/mL), low fibrinogen (56 mg/dL) and normal bone marrow (no hemophagocytosis or malignancy). Flow cytometry for perforin and lymphocytic subset assay were normal (CD19+17 %, CD3+72 %, CD3 +/CD4+35 %, CD3+/CD8+33 %, NK cells 8 %). The laboratory parameters of the patient are summarized in Table 1.

On day 18, a diagnosis of CMV associated HLH was made as per HLH 2004 protocol. He was started on dexamethasone (10 mg/m²/day) and etoposide following which all the clinical and laboratory parameters improved. Ganciclovir was discontinued after 14 days of intensive therapy as plasma quantitative CMV DNA PCR showed viral load below 57.1 copies/mL and the patient was discharged on day 23. He was treated with dexamethasone and etoposide for 8 weeks. On follow up, he is doing well with a normal BERA.

Discussion

Our patient presented with pneumonia, hepatosplenomegaly, bicytopenia, seizures and biochemical hepatitis. These features were consistent with severe CMV disease reported in the literature [5]. CMV IgM is a less reliable investigation. Hence, CMV infection was confirmed with most specific CMV DNA PCR assay. There was a remote possibility of congenital infection as he was previously healthy. Persistent hectic fever unresponsive to broad spectrum antibiotics, bicytopenia and increasing hepatosplenomegaly without

Table 2 Diagnostic criteria for HLH fulfilled in index case

2004 diagnostic criteria for HLH	Criteria fulfilled in index case
Clinical criteria	
Fever	Yes
Splenomegaly	Yes
Laboratory criteria	
Cytopenia (affecting ≥ 2 cell lines in the peripheral blood)	Yes
Fibrinogen <1.5 g/L and/or Hypertriglyceridemia	Yes
Histopathological criteria	
Hemophagocytosis in bone marrow or spleen or lymph node	No
No evidence of malignancy	
Additional criteria	
Low or absent NK cell activity	No
Ferritin >500 $\mu\text{g/dL}$	Yes
Soluble CD 25 (i.e. IL 2 receptor) $\geq 2,400$ U/mL	Not done

evidence of any concurrent bacterial, fungal or parasitic infection made us think of sHLH. Infant met 5 out of 8 HLH 2004 diagnostic criteria (Table 2) [1]. EBV PCR for concurrent etiology of HLH and Interleukin 2 receptor level were not done because of financial constraints.

HLH may develop as a result of uncontrolled T cell and macrophage activation with hypercytokinemia (in particular- $\text{IFN}\gamma$, $\text{TNF}\alpha$, IL-1, IL-2, IL 6, and IL 18); which may be caused by a severe infection. Virus associated HLH was mostly described in immunocompromised; but in immunocompetent host it was rarely reported [6]. Epstein–Barr virus, adenovirus, human herpes virus 8 were among the few viruses described with HLH [1–3]. Although, CMV may precipitate FHL and sHLH [2]; CMV-HLH was rarely reported in immunocompetent infants and children [6–9].

The clinical presentation of our patient was similar to previous reports but differed in certain aspects; rash and lymphadenopathy was described in majority [6, 7] whereas our patient had convulsions. FHL and sHLH both present with clinically indistinguishable features. Patients with FHL generally show reduced NK activity, perforin deficiency and persistent or recurring HLH [2, 4]; although the same was not seen in our case. Moreover, our patient responded to only two drugs (dexamethasone and etoposide) and disease is in remission, without relapse for 12 months after treatment was completed. There was no family history suggestive of FHL in the patient. Still, FHL cannot be ruled out in this case; as the patient's age favours it, family history can be negative in FHL as the disease follow recessive pattern and genetic investigations for

excluding FHL (*PRF1*, *UNC13D*, *STX11* or *STXBP2*) could not be done because of lack of availability [1–4]. Considering all these points, CMV induced secondary HLH was thought, at the same time, possibility of FHL could not be ruled out. HLH following breast-milk transmitted CMV was reported in the preterm infants [10]; supporting our case wherein breast feeding might be a cause responsible for CMV transmission in addition to an intrauterine transmission.

HLH 2004 treatment protocol includes use of corticosteroids, etoposide and/or immunosuppressive agents such as cyclosporine and IV immunoglobulins. Stem cell transplantation is recommended in the case of documented familial HLH, recurrent or progressive disease despite intensive therapy [1, 2]. We modified HLH therapy with least nephrotoxic regimen (dexamethasone, etoposide) as he was to receive ganciclovir simultaneously. Intrathecal methotrexate (IT MTX) should be included in HLH treatment if the first 2 weeks of therapy fails to improve neurological symptoms (i.e. for progressive neurological symptoms). Our patient responded to the treatment with a very good clinical and laboratory outcome not necessitating the use of IT MTX.

HLH may pose a diagnostic challenge in the proven case of severe CMV infection as both have overlapping clinical features as was noted in our patient. Early diagnosis and prompt treatment of HLH in such case can only reverse the disease process.

Conclusion

HLH could be a serious complication of CMV even in immunocompetent infant; and should always be suspected in the differential diagnosis of any sepsis like illness presenting with unremitting fever, hepatosplenomegaly and cytopenia (decline in any two cell lines). Prognosis is better with the earliest initiation of treatment for the underlying cause and chemotherapy, particularly in secondary HLH.

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