Hemi-meningitis with hemophagocytic lymphohistiocytosis

Ozan Kocak, Coskun Yarar, Sevgi Yimenicioğlu[1], Arzu Ekici[2], Özcan Bör[3]

Departments of Pediatric Neurology, and [3]Pediatric Hematology, Eskisehir Osmangazi University Hospital, Eskisehir, [1]Department of Pediatric Neurology, Eskişehir State Hospital, Eskisehir, [2]Department of Pediatric Neurology, Bursa Sevket Yilmaz Education and Research Hospital, Bursa, Turkey

Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare lymphoproliferative disorder. HLH may occur as a complication of Epstein-Barr virus (EBV), particularly in patients with immunodeficiencies. Herein, we describe a 16-year-old girl with neurological complications associated EBV-induced HLH. Her cerebral magnetic resonance imaging (MRI) showed contrast-enhanced axial T1-weighted images with enhancement of meningeal surface in the right hemisphere that was consistent with right hemi-meningitis. Hydrocephalus, dilated subdural spaces, delayed myelination, edema, diffuse parenchymal atrophy, calcifications, diffuse/patchy white matter abnormalities have all been previously described with HLH. To the best of our knowledge, this is the first case of hemi-meningitis associated with HLH. We suggest that clinicians should consider HLH with vascular disorders when they determine unilateral meningitis on a brain MRI.

Key Words

Epstein-Barr virus, hemi-meningitis, hemophagocytic lymphohistiocytosis, hemophagocytic syndrome

For correspondence:
Dr. Ozan Kocak, Department of Pediatric Neurology, Eskisehir Osmangazi University Hospital, Meselik, Eskisehir, Turkey.
E-mail: ozankocak79@gmail.com

Ann Indian Acad Neurol 2016;19:388-391

Introduction

Childhood Epstein-Barr virus (EBV) infection has a large clinical spectrum, ranging from asymptomatic infections to life-threatening lymphoproliferative disease, Burkitt lymphoma, nasopharyngeal carcinoma, and B-cell lymphoma. Hemophagocytic lymphohistiocytosis (HLH) is a rare complication of EBV infection. Typical signs and symptoms include fever, hepatosplenomegaly, lymphadenopathy, rash, and neurological symptoms. Laboratory findings include cytopenia, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, coagulation abnormalities, elevated transaminases, elevated cerebrospinal fluid (CSF) protein, and pleocytosis.[1,2] It can result in multiple organ dysfunctions and a mortality rate of approximately 30%.[3] Although EBV-induced HLH carries a high mortality rate, with early diagnosis and treatment, the patient may completely recover. Central nervous system involvement may occur at presentation or during the course of HLH. We present a girl with EBV-induced HLH who had hemiparesis and hemi-meningitis on cerebral MRI.

Access this article online	
Quick Response Code:	Website: www.annalsofian.org
	DOI: 10.4103/0972-2327.165458

Case Report

A 16-year-old girl was admitted to our hospital because of left hemiparesis and altered consciousness for about one day. Two days before admission, she had a nasal discharge, vomiting, fever, and a headache, without seizures. She had never had any neurological or infectious disease before, nor did she have a family history of neurological disease. Physical examination revealed temperature of 39°C, pulse of 86 beats/min, blood pressure of 144/76 mm Hg, and respiratory rate of 24 breaths/min. Her head circumference was 52 cm (25-50th percentile), her body weight was 70 kg (75-90th percentile), and her height was 165 cm (50-75th percentile). Her body weight for height exceeded the standard deviation. The initial neurologic examination revealed a lethargic state with signs of meningeal irritation, hypoactive deep tendon reflexes, muscle weakness, and positive Babinski sign on left side. She had hepatosplenomegaly measured at 3 cm at the costal margin.

The laboratory data obtained on admission are listed in Table 1. CSF examination revealed protein at 48 mg/dL, glucose at 45 mg/dL, 30 leukocyte/mm^3, and the polymerase chain reaction for HSV Type 1 and CSF bacterial culture were negative. Antinuclear antibody, rheumatoid factor,

antineutrophil cytoplasmic antibody were all negative and serum immunoglobulins levels were normal.

The cerebral MRI showed contrast-enhanced axial T1-weighted images with enhancement of meningeal surface in the right hemisphere that was consistent with right hemi-meningitis [Figure 1]. The patient's electroencephalogram was normal. Vancomycin, cefotaxime, and acyclovir infusions were started. Acyclovir was stopped when CSF HSV Type 1 PCR became negative. On the fifth day of treatment, vancomycin-related red-man syndrome developed, so the treatment was stopped. There were partial recurrent seizures on her left arm, which were controlled with an IV midazolam infusion and oral valproic acid treatment. Her antibiotic treatment stopped on the 14th day of treatment, and her examination was nearly normal; however, on the 15th day of admission, her fever and sedimentation increased again. Her laboratory results showed severe neutropenia (absolute neutrophil count: 0.0/µl) and anemia [Table 1]. Because the peripheral blood smear showed increased monocytes, and she also had hepatomegaly, bicytopenia with elevated serum lactate dehydrogenase and triglyceride levels, bone marrow aspiration (BMA) was performed. The BMA revealed a hypercellular marrow, without hemophagocytosis. Meropenem, amikacin, and amphotericin treatment were given. Hypermetabolic lymph nodes on the left cervical and bilateral axillar regions were shown on the positron emission tomography-computed tomography. Her symptoms and laboratory findings were strongly consistent with HLH; therefore BMA was repeated, and the smear showed an increased number of histiocytes with hemophagocytosis [Figure 2]. In serologic examination, EBV VCA IgM became positive. The patient met the diagnostic criteria of HLH, and she recovered completely with steroid and intravenous immunoglobulin (IVIG) treatment.

Table 1: Laboratory features of patient

Parameters	On admission	Day 15	Normal value
Hemoglobin (g/dL)	9.6	8,2	12–14
Leukocytes (×10^3/ul)	13400	1800	4500-13000
Absolute neutrophils (×10^{3}ul)	12.3	0.0	>2,5
Platelets (×10^3/ul)	227000	387000	250000-350000
Prothrombin time (sec)	14.8	11.6	9.4-15.4
Activated partial thromboplastin time (sec)	30.5	27.5	26-36
International normalized ratio	1.1	1.012	0,8-1,2
Fibrinogen (mg/dL)	756	99,1	200-400
D-dimer (µg/dL)	0,23	0,17	0-0,55
Total protein (g/dL)	7.1	6.8	6-8,5
Albumin (g/dL)	3.9	3.6	3,5-5,2
Total bilirubin (mg/dL)	0.25	0.34	0-1
Direct bilirubin (mg/dL)	0.1	0.15	0,-0,2
Aspartate aminotransferase (U/L)	35.9	38	0-40
Alanine aminotransferase (U/L)	26.8	36.8	0-33
Lactate dehydrogenase (U/L)	5070	1126	240-480
Compleman 3 (mg/dL)	99		90-130
Compleman 4 (mg/dL)	17.1		10-40
Ferritin (ng/ml)	137	423	13-150
Triglycerides (mg/dl)	134	466	0-200
Antinuclear antibody	negative	negative	
Antineutrophil cytoplasmic antibody	negative	negative	
Sedimentation rate (mm/h)	119	138	0-10
C–reactive protein (mg/dl)	4.48	3.42	0-0.8

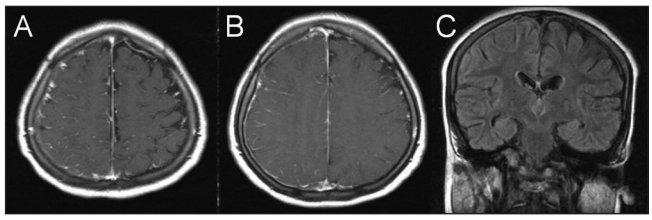

Figure 1: (a, b) Contrast-enhanced axial T1-weighted images showing enhancement of meningeal surface at the right hemisphere. (c) Asymmetrical sulcal involvement seen on the right side on the coronal FLAIR image

Discussion

HLH occurs in two forms, primary and secondary. Primary HLH has a genetic etiology, and most patients with primary HLH develop the disease under one year of age, but it can also be developed in early adulthood. Secondary HLH has been associated with immunologic disorders, malignancies, or infectious diseases. Criteria for diagnosis of HLH include clinical, laboratory, and histopathological findings. A molecular diagnosis (Mutation of PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A, BIRC4) or at least five of the following criteria should be satisfied for diagnosis: Fever, splenomegaly, cytopenia in at least two cell lines, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in tissue biopsy, low or absent NK-cell activity, elevated ferritin concentration >500 ng/dL, or elevated soluble CD25 (soluble IL-2 receptor) >2400 ng/dL.[2]

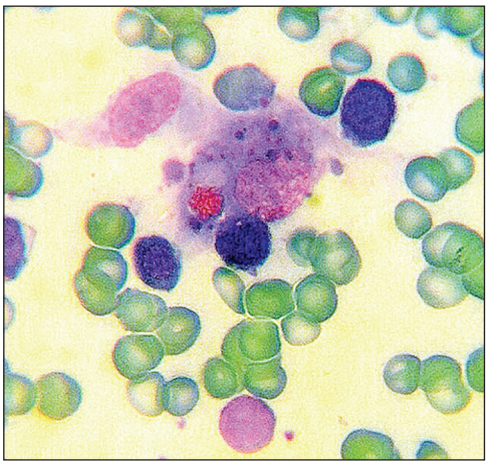

Figure 2: Bone marrow evaluation revealed a hypocellular marrow with active hemophagocytosis

EBV-induced HLH can affect infants to young adults and occurs more commonly in Asian individuals and in patients with immunodeficiencies. Pathophysiology of EBV-induced HLH has not been fully elucidated, but cytokine-mediated activation of macrophages probably predisposes people to the development of HLH. Three mechanisms were proposed regarding the pathophysiology of EBV-induced HLH: a) The latent membrane protein 1 (LMP1) of the EBV regulates its own expression and the expression of human genes, and it was shown to up-regulate the tumor necrosis factor-α (TNF-α) resulting in macrophage activation;[4] b) EBV can infect B cells, triggering a polyclonal proliferation of cytotoxic T lymphocytes, which in turn stimulates histiocytes and macrophages, resulting in uncontrolled immune activation and hypercytokinemia;[5] c) EBV targets CD8 T cells and natural killer cells, which leads to rapid, uncontrolled proliferation and major release of high levels of IL-2, interferon, TNF-α, and IL-6, among other inflammatory cytokines, as a result of widespread lymphohistiocytic activation.[2,3,6]

For HLH-2004, treatment includes an initial eight-week course, including etoposide, dexamethasone, intravenous immunoglobulin (IVIG), and cyclosporine, and selected patients with evidence of central nervous system (CNS) disease receive intrathecal therapy with methotrexate and prednisolone.[2] The initial treatment duration should be limited to eight weeks, and the patient's response should be evaluated at four and eight weeks. Patients may be treated first with corticosteroids/IVIG, but if the response is poor, it is recommended that the patient be promptly switched to an etoposide-containing regimen within four weeks of diagnosis.[3]

Involvement of CNS was reported in different studies, occurring either at presentation or during the course of HLH.[7,8]. Incidence of neurologic involvement of HLH was reported in 10% to 73% of cases.[7-9] HLH has variable clinical presentations and neuroimaging findings. Neurologic findings include irritability, seizures, cranial nerve palsies, ataxia, nystagmus, delayed psychomotor development, meningeal signs and evidence of increased intracranial pressure, neurologic symptoms including hypotonia or hypertonia, meningismus, seizures, coma with opisthotonic posture, and abnormal cardiac or respiratory rates.[7,9]

Abnormal neuroradiological findings in HLH correlate well with the clinical severity of clinical manifestations. The most frequent findings on CTs are hydrocephalus, dilated subdural spaces, edema, diffuse parenchymal atrophy, multiple hyperdense areas, and calcifications. MRIs show delayed myelination, parenchymal atrophy and diffuse white matter or patchy increased signal abnormalities, diffuse leptomeningeal and perivascular enhancement, enlargement of ventricles, and extra-axial fluid spaces. CSF examination generally reveals pleocytosis and elevated protein levels.[7,9,10,11] Patients with EBV-HLH may develop primary CNS disease presenting as a CNS white matter disease, such as through spotty T2 high signals in the white matter of the brain on MRI that are similar to acute disseminated encephalomyelitis.[10,11]

EBV-induced HLH can be fatal, but spontaneous recoveries can be seen. Prognostic factors for EBV-induced HLH in children are not yet well-described. A few parameters were previously identified that are associated with poor clinical outcome: Older age, hypoalbuminemia, EBV reactivation, hyperbilirubinemia, hyperferritinemia, and multidrug chemotherapy.[12,13] Trottestam *et al*., also reported that hyperbilirubinemia, hyperferritinemia and CSF pleocytosis at onset, and persisting fever, anemia thrombocytopenia, and hyperferritinemia two weeks after the initiation of treatment were significantly associated with poor outcomes.[14]

Our patient is 16 years old, and there is no history of recurrent/severe infectious diseases or any neurologic disease. She first presented with fever and neurologic signs (altered mental status, hemiparesis), and then splenomegaly, bicytopenia, hypertriglyceridemia/hypofibrinogenemia, hemophagocytosis on bone marrow, and seizures occurred. She met five criteria for HLH. Diagnosis of EBV infection was performed by serologic testing. She had hyperferritinemia at the time of diagnosis, which is a prognostic factor for poor clinical outcomes. Nevertheless, she completely recovered with IVIG and steroids. The most interesting features of our case were the MRI findings. Cerebral MRI showed unilateral contrast-enhanced axial T1-weighted images and enhancement of the meningeal surface at the right hemisphere, which is consistent with hemi-meningitis. Hemi-meningitis is an unusual disease, and the unilateral nature of the meningitis suggests a vascular etiology, such as Wegener granulomatosis.[15] To the best of our knowledge, this is the first case of EBV-HLH with hemi-meningitis without a vascular etiology.

In conclusion, EBV-associated HLH has a high mortality rate, and early diagnosis and treatment are important. HLH generally presents with typical sign and symptoms, but occasionally neurologic signs and symptoms can be primary. This is a single case, but we suggest that clinicians consider HLH when they determine unilateral meningitis on a brain MRI.

References

1. Patil AK, Azad ZR, Mathew V, Alexander M. Chronic meningitis and central nervous system vasculopathy related to Epstein Barr virus. Ann Indian Acad Neurol 2012;15:303-6.
2. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, *et al*. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124-31.
3. Imashuku S. Clinical features and treatment strategies of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. Crit Rev Oncol Hematol 2002;44:259-72.
4. Lay JD, Chuang SE, Rowe M, Su IJ. Epstein-barr virus latent membrane protein-1 mediates upregulation of tumor necrosis factor-alpha in EBV-infected T cells: Implications for the pathogenesis of hemophagocytic syndrome. J Biomed Sci 2003;10:146-55.
5. Pratt ZL, Zhang J, Sugden B. The latent membrane protein 1 (LMP1) oncogene of Epstein-Barr virus can simultaneously induce and inhibit apoptosis in B cells. J Virol 2012;86:4380-93.
6. Vince A, Lepej SZ, Kurelac I, Barsic B, Kozic S, Klinar I, *et al*. Virological and immunological characteristics of fatal Epstein-Barr virus mononucleosis in a 17-year-old Caucasian male presenting with meningoencephalitis and hemophagocytic syndrome. J Neurovirol 2007;13:389-96.

7. Haddad E, Sulis ML, Jabado N, Blanche S, Fischer A, Tardieu M. Frequency and severity of central nervous system lesions in hemophagocytic lymphohistiocytosis. Blood 1997;89:794-800.
8. Jovanovic A, Kuzmanovic M, Kravljanac R, Micic D, Jovic M, Gazikalovic S, *et al*. Central nervous system involvement in hemophagocytic lymphohistiocytosis: A single-center experience. Pediatr Neurol 2014;50:233-7.
9. Henter JI, Nennesmo I. Neuropathologic findings and neurologic symptoms in twenty-three children with hemophagocytic lymphohistiocytosis. J Pediatr 1997;130:358-65.
10. Forbes KP, Collie DA, Parker A. CNS involvement of virus-associated hemophagocytic syndrome: MR imaging appearance. AJNR Am J Neuroradiol 2000;21:1248-50.
11. Fitzgerald NE, Mac Clain KL. Imaging characteristics of hemophagocytic lymphohistiocytosis. Pediatr Radiol 2003;33:392-401.
12. Ishii E, Ohga S, Imashuku S, Yasukawa M, Tsuda H, Miura I, *et al*. Nationwide survey of hemophagocytic lymphohistiocytosis in Japan. Int J Hematol 2007;86:58-65.
13. Kogawa K, Sato H, Asano T, Ohga S, Kudo K, Morimoto A, *et al*. Prognostic factors of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in children: Report of the Japan Histiocytosis Study Group. Pediatr Blood Cancer 2014;61:1257-62.
14. Trottestam H, Berglo¨f E, Horne A, Onelöv E, Beutel K, Lehmberg K, *et al*. Risk factors for early death in children with hemophagocytic lymphohistiocytosis. Acta Paediatr 2012;101:313-8.
15. Wingerchuk DM, Dyck PJ, Mertz LE. Hemi-meningitis: A focal sign heralding a multisystem necrotizing vasculitis. Neurology 2008;70:2014.

How to cite this article: Kocak O, Yarar C, Yimenicioğlu S, Ekici A, Bör Ö. Hemi-meningitis with hemophagocytic lymphohistiocytosis. Ann Indian Acad Neurol 2016;19:388-91.
Received: 04-02-15, **Revised:** 07-04-15, **Accepted:** 05-06-15
Source of Support: Nil, **Conflict of Interest:** None declared.