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Case Report

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Epstein-Barr Virus-Induced Hemophagocytic Lymphohistiocytosis

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is one of the complications of Epstein-Barr virus (EBV) infection. Although the patients who have developed HLH following EBV have normal immune system, there are a few patients with EBV-induced immune deficiency who develop HLH as well. Here, we describe the case of a 10-year-old girl with neurological complications caused by EBV-induced HLH. The patient received rituximab, leading to weakening inflammation associated with EBV infection and suppression of disease through quick treatment.

KEY WORDS: X-Linked lymphoproliferative disease, Hemophagocytic lymphohistiocytosis, Systemic inflammatory response syndrome, Infectious mononucleosis, Epstein - Barr virus, Etanercept

INTRODUCTION

The Epstein–Barr virus (EBV) infects B cells. In most cases, EBV-positive patients develop a severe form of infectious mononucleosis which typically manifests with fever, tonsillopharyngitis, lymphadenopathy and hepatosplenomegaly. HLH is a rare complication of Epstein-Barr virus *(*EBV) infection. Deficiencies may be characterized by abnormal activity of lymphocyte function leading to hemophagocytosis and multi-organ failure. Although EBV-associated HLH carries a high mortality rate, quick diagnosis and appropriate treatment can subside the disease.

We describe here a patient who developed hepatosplenomegaly and pancytopenia at 2 years of age but achieved automatic recovery. There was no neurological manifestation. At age 10, there was a clinical suspicion of EBV-induced HLH and the patient was given the option of treatment with rituximab.

INTRODUCING THE CASE

A ten-year-old girl diagnosed with pneumonia admitted to the hospital. She received antibiotic treatment due to fever and chills. During the hospitalization period, the patient recovered and developed hemophagocytosis with pancytopenia as well as sores on the lip. The patient underwent BMA and nothing abnormal was found. In spite of treatment, the disease did not subside and she developed fever, abdominal distention and edema in her lower extremities. The patient was then transferred to another hospital and was reexamined once again. Physical examination showed that the patient had decreased deep-tendon reflexes (DTR) and was unable to walk. Brain CT scan revealed that the cerebral ventricles were surrounded by a hypodense area. A chest CT-scan showed the right-sided pleural effusion. A CT scan of the abdomen showed severe hepatosplenomegaly. The patient was positive for EBV antibody. Clindamycin,

ceftazidime, dexamethasone, IVIG (intravenous immunoglobulin) and G-CSF were administered. Since the patient did not achieve full recovery, she was transferred to our center. Based on clinical symptoms and lab tests (Table 1), BMA was performed once again and the result raised suspicion of EBV-induced secondary HLH. Rituximab was injected once and the patient developed a blood EBV load of zero within one week. In order to control abnormal stimulation of the immune system, HLH-2004 protocol was used. Full recovery was achieved by the patient. EBV PCR was immediately checked and rituximab therapy was discontinued. Serum Immunoglobulin levels were low during the treatment process. The patient was investigated for mutations in IL-2-inducible T cell kinase (ITK) and negative test results were received. (The patient was negative for mutations in IL-2-inducible T cell kinase (ITK)). She is now considered to be an acceptable candidate for transplantation from an HLA matched sibling donor.

Table1: Laboratory Values on Admission

WBC	1100/mm^2	Ceruloplasmin	NL
N	387	ANA	-
L	-	ds DNA	-
Mono	-	Ig (Before IVIG)	
Hb	8.7/gLbs	IgM	0
HCT	24.2%	IgG	27.1
PLT	32000	IgA	25
LDH	610	IgE	7.5
BS	126	EBV DNA (PBS)	9850
BUN	14	Ig (Before IVIG)	
Cr	0.5	IgM	0
Na	138	IgG	27.1
K	4.3	IgA	25
Ca	9.2	IgE	7.5
P	3.4	EBV DNA (PBS)	9850
SGOT	50	LP	
SGPT	253	WBC	0
Bil	1.3	RBC	0
Bilin	0.1	Pr	NL
Urea	26	GLo	NL
Fibrinogen	1	PT	13
Ferritine	1159	PTT	37
T	200	Deb Test	NL
Chol	180		
Cu	117		

DISCUSSION

HLH was first described in 1939. HLH can be divided into two subgroups: primary or familial HLH and secondary HLH. The primary form is an inflammatory disease which is similar to secondary one on the basis of symptoms.[3] Primary HLH usually arises in young children less than one year old (70% cases); however, in rare cases it can also occur in adults (Perforin gene mutations have been identified in patients with primary HLH).[4] Five types of gene mutations have been identified in patients with primary HLH. For example, Type 2 is caused by mutations in genes 21-22 and Type 5 is due to mutations in the MUNC18-20 that may be accompanied by hypogammaglobulinemia.[5] Hypogammaglobulinemia was not confirmed in the patient because it was not possible to check mutation (the related tests were sent to Germany to examine the type 5 disease). EBV may also be accompanied by hypogammaglobulinemia for a certain period

Secondary HLH is associated with immunologic stimulation caused by malignancies and bacterial or congenital infections. The most common causes of secondary HLH are viral infections by EBV, CMV, ProB19 and HIV. EBV-related secondary HLH may occur at any age. A secondary form of HLH may also occur in patients with normal immune systems. However, it may also be seen in patients with immune system defects.[3], 4 Secondary HLH is a known complication of EBV infection, particularly in patients with x-linked lymphoproliferative disease.[5] The incidence of X-linked lymphoproliferative syndrome is 1 in 1,000,000 male infants.[6, 7]

Diagnostic criteria for HLH disease are listed in Table2.

Table2. Diagnostic criteria for HLH disease

*** Major Criteria:**
1. Fever of >38.6 Degrees centigrade
2. Splenomegaly
3. Cytopenia involving >= 2 cell lines
4. Hyper Triglyceridemia or Hypofibrinogenemia
5. Hemophagocytosis demonstrated in bone marrow, spleen or lymph node without evidence of malignancy

*** Alternative criteria**
1. Low or absent Nk cell activity
2. Serum ferritin level of >500
3. Soluble CD_{29} (soluble IL-2 receptor) level at >2400

diagnosis of HLH requires the presence of all 5 major criteria. If the patient meets only 4criteria but the clinical suspicion for HLH is high, one should initiate treatment,
Because delays may be fatal.
Alternative criteria 1 or a combination of 2 and 3 may substitute for 1 major criterion.
Adapted from Henter JI,Elinder G,Ost A.Semin Oncol. 1991; 18:29-33.

Precise mechanism of EBV-induced HLH has recently been found. It means that EBV-infected B

cells stimulate cytotoxic T lymphocytes leading to hypercytokinemia and stimulation of histolytic cells.[9, 10] More recently, it has been found that chronic stimulation by EBV may cause chronic HLH in the patient. On the other hand, EBV causes stimulation, generation and uncontrolled secretion of T-and NK- cells, as well as generation of IL2, INFa and IL6. These materials are said to be responsible for Hemophagocytic lymphohistiocytosis. There is another mechanism by which EBV stimulates membrane protein (LMP-1) in cells. The cells exceedingly secrete INFa, leading to macrophages. Similar to XLP, LMP-1 may cause acquired immune deficiency, leading to HLH accordingly.[13, 14]

Treatment follows two goals: first, to suppress immune response using IVIG, steroid and HLH protocol. Second, to inhibit undesirable influence of immune response and cytokine-stimulated cell activation using immunochemotherapy. In cases with neurological symptoms, immunochemotherapy is required. The level of viral DNA which is measured by quantitative PCR may be useful to demonstrate treatment response predicting mortality. The DNA level reached zero in our patient. Using IVIG prior to start of protocol 2004[2] may be regarded as an appropriate treatment, raising living hope. It has also been recommended in the treatment of EBV-induced secondary HLH monthly.[2]

Rituximab may be a useful treatment for decreasing mortality. Decrease of B cells, which have been contaminated by EBV, actually causes decrease of viruses,[16] as it may be useful for our patient as well. However, it has no significant effect on T cells. The effect of anti-INFa has not been confirmed yet. Finally, treatment-refractory patients, transplant candidates, patients with familial type of HLH, or recurrent disease undergo chemotherapy for 8 weeks. Patients who respond favorably to treatment do not undergo transplantation but those who experience relapse and exhibit neurological symptoms are considered for transplantation.

CONCLUSION

Severe infection of EBV is not associated with life-threatening condition, but our case study needs urgent treatment. In patients with long-term EBV infection, pancytopenia, coagulopathy and hepatosplenomegaly, the existence of the secondary HLH is in doubt. To confirm the diagnosis, BMA will be performed and the serum ferritin level will be measured as well. For patients with secondary HLH, initial therapy with the HLH-2004 protocol[17] approach is appropriate. Rituximab can be used when HLH is associated with EBV to inhibit the immune response. Thus, the main aim of treatment is to reduce the rate of mortality in patients with HLH.

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