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Case Report

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Aggressive Progression and Chemotherapy Resistance of Fulminant Epstein-Barr Virus-Associated Hemophagocytic Lymphohistiocytosis

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Abstract

Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH) is a rare, life-threatening disease that develops mostly in children. Here we report the case of a 28-year-old woman in whom EBV-HLH followed a fatal course despite chemotherapy. She was referred to our hospital with fever and anorexia. Blood tests revealed leukopenia, thrombocytopenia, and elevated ferritin. Bone marrow aspiration showed hemophagocytic syndrome. She received methylprednisolone pulse therapy, but this was ineffective. A high EBV viral load was identified, indicating EBV-HLH. She was treated with etoposide and high-dose dexamethasone-containing chemotherapy, but respiratory condition worsened due to interstitial pneumonia. Despite ventilator management, she died on hospital day 11. EBV-HLH in young adults exacerbates rapidly and has a high mortality rate. Effective treatments are needed for EBV-HLH in young adults.

Keywords: Epstein-Barr virus (EBV); Hemophagocytic lymphohistiocytosis (HLH); Young Adult.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH), also known as hemophagocytic syndrome, is a rare clinical syndrome characterized by abnormal proliferation and activation of reactive mononuclear phagocytic cells, cytotoxic T-lymphocytes or natural killer cells, and is associated with increased levels of inflammatory cytokines. HLH is classified into primary HLH, represented by familial HLH, and secondary HLH induced by infections, tumors, and autoimmune diseases. This pathology often occurs in childhood, but cases in young adults have been recognized [1,2]. Epstein-Barr Virus (EBV) is a member of the human herpesvirus genus, and is the causative agent for around half of infection-associated HLH [3,4], and the most common cause in Japan [5]. In particular, fatal EBV-associated HLH (EBV-HLH) arises in the setting of acute EBV infection. Most cases have been reported in Asia, and this entity portends an abysmal prognosis with nearly 100% mortality [6]. Etoposide is considered a key drug and is often treated according to the HLH-2004 protocol in children [7,8], but no standard treatment has been defined for young adults and various treatments are therefore used [9-11].

We report herein the case of a young adult woman in whom EBV-HLH followed a fatal course despite etoposide and high-dose dexamethasone-containing chemotherapy.

Case report

A 28-year-old woman was referred to our hospital with a 3-day history of high fever and loss of appetite. She had no familial or personal history suggestive of immunodeficiency. Leukopenia and mild thrombocytopenia were observed on blood tests, but no Disseminated Intravascular Coagulation (DIC) was apparent (Table 1). Computed Tomography (CT) showed hepatosplenomegaly, but no lymphadenopathy or inflammatory findings such as pneumonia. The patient was hospitalized and received drip infusion of antibiotics, but fever continued even on hospital day 4. Blood testing revealed progression of pancytopenia (white blood cell count, 1100 /μL; hemoglobin level, 10.6 g/dL; platelet count, 13,000 / μL). Based on the prolonged Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) and elevated Fibrinogen/ Fibrin Degradation Product (FDP) levels (104.1 μg/mL), DIC was diagnosed. Bone marrow aspiration showed increased monocytes and macrophages (Figure 1A), and a characteristic hemophagocytic image (Figure 1B). Flow cytometry found that CD8- and HLA-DR-positive, CD4-negative T-cells accounted for 84.3% of total lymphocytes. G-banding showed normal karyotype. Based on the difficulty encountered achieving hemostasis after bone marrow aspiration, antibiotic-refractory symptoms, and no evidence of bacterial infection in blood and urine cultures and additional examinations, HLH and DIC were diagnosed. The clinical course is shown in Figure 2. The patient was initially treated with methylprednisolone pulse (1000 mg/day) for 3 days. However, fever persisted, and pancytopenia and liver dysfunction continued to worsen daily. Platelets and fresh frozen plasma were transfused to maintain blood levels, but worsening DIC necessitated fibrinogen transfusion. Ferritin levels were markedly elevated to 16,009 ng/mL, soluble interleukin (IL)-2 receptor was elevated to 26,400 U/mL. anti-EBV-VCA immunoglobulin (Ig)G and IgM were slightly positive, EBV nuclear antigen (EBNA) was negative, and EBV-DNA load in peripheral blood was markedly elevated to 520,000 copies/mL. As a result, EBV-HLH associated with primary EBV infection was diagnosed. Cyclophosphamide, high-dose cytarabine, etoposide and high-dose dexamethasone (CHASE) therapy was started on hospital day 7. However, on hospital day 9, blood oxygenation could not be maintained, and interstitial pneumonia was diagnosed after chest X-rays showed interstitial shadows in both lungs. The patient required ventilation to maintain blood oxygenation. On hospital day 10, consciousness disorder appeared and she complained of strong pain, and morphine hydrocholoride was therefore initiated. Blood transfusion was terminated because of the transition to palliative treatment. The patient died on hospital day 11. Cytokine tests performed with residual serum after death showed increased inflammatory cytokines such as interferon (IFN)-γ, IL-6, and tumor necrosis factor (TNF)-α, confirming the presence of cytokine storm (Table 1).

Discussion

EBV-HLH is the most common infectious disease-related HLH [3-5]. EBV-HLH in children is expected to show a long-term survival rate of about 60-70% as a result of treatment using the HLH-2004 protocol and allogeneic hematopoietic stem cell transplantation [7,8], but no standard treatment has been defined for adults. HLH associated with EBV often follows an aggressive course, with a high mortality rate of 80-95% [6,10,11]. Etoposide is considered a key drug, so in this case CHASE therapy was administered the time of data deterioration as an etoposide-containing chemotherapy, but disease progression could not be suppressed and death occurred.

The recent novel coronavirus disease 2019 (COVID-19) pandemic bears a resemblance to EBV-HLH in terms of its association with cytokine storm [12]. Dexamethasone has been observed to be effective in severe cases of COVID-19, resulting in suppression of cytokine storm [13]. However, no such effect was observed in this case of EBV-HLH. Increased levels of inflammatory cytokines were also observed in this case, which may have caused worsening of the condition due to the cytokine storm. Plasmapheresis may be effective as a method when chemotherapy is ineffective. Plasmapheresis has been reported to be effective in COVID-19 [14].

Since clinical application of anti-cytokine preparations has become possible for HLH, the use of anti-TNF-α preparations, anti-IFN-γ preparations, anti-IL-6 antibodies, and Janus kinase (JAK) 1/2 inhibitors has been investigated [15-17]. In particular, ruxolitinib has recently undergone various trials, and clinical results have been accumulated. The present case may also have been improved by the administration of these drugs.

Conclusion

EBV-HLH associated with primary EBV infection in young adult is a disease with poor prognosis. It is hoped that standard treatments will be established in the accumulation of new drug treatment strategies.

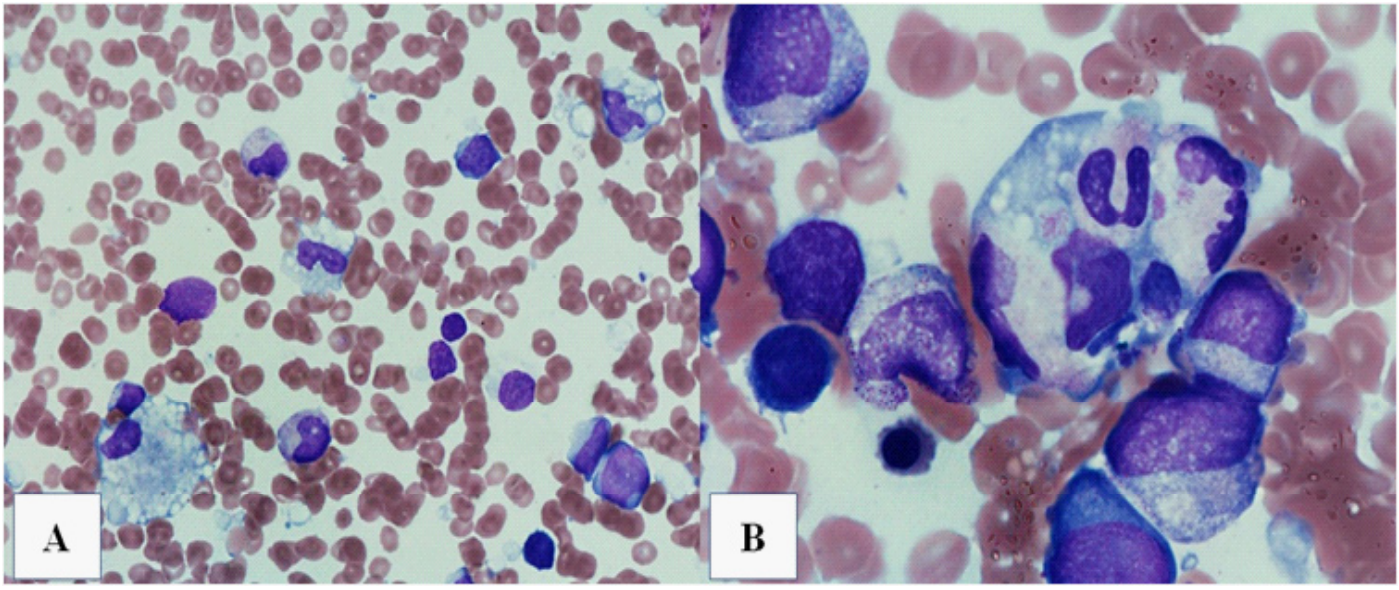

Figure 1: A) Bone marrow aspirate shows increased monocytes and macrophages. Pappenheim stain, ×100 magnification. B) Characteristic hemophagocytic findings are seen. Pappenheim stain, ×1000 magnification.

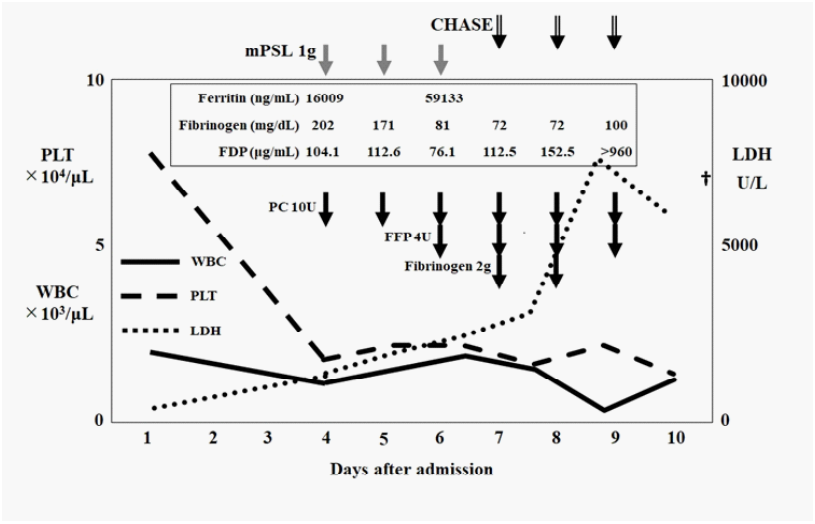

Figure 2: Clinical course after admission. WBC, white blood cells; PLT, platelets; LDH, lactate dehydrogenase; PC, platelet concentrates; FFP, fresh frozen plasma; FDP, fibrinogen/fibrin degradation product; mPSL, methylprednisolone; CHASE, cyclophosphamide, high-dose cytarabine, etoposide and high-dose dexamethasone.

Table 1: Laboratory findings on admission.

Complete blood count		Biochemistry		Immunology	
White Blood Cells	2100/μL (3300-8600)	T-Bil	0.9 mg/dL	EBV VCA-IgG	0.8 (+-)
band	15%	AST	36 U/L	EBV VCA-IgM	0.6 (+-)
segment	59%	ALT	40 U/L (7-23)	EBNA	0.4 (-)
monocyte	4%	LDH	282 U/L (124-222)	CMV IgG	3.1 (+-)
lymphocyte	22%	γ-GTP	23 U/L	CMV IgM	0.38 (-)
Red Blood Cells	501×10^4/μL	Amylase	37 U/L	ANA	<40
Hemoglobin	14.3 g/dL	TP	7.3 g/dL	PR3-ANCA	<1.0
Hematocrit	42.50%	Alb	4.3 g/dL	MPO-ANCA	<1.0
Platelets	8.8×10^4/μL (15.8-34.8)	BUN	7 mg/dL	anti CL-β2GP1 Ab	<1.2
		Cr	0.64 mg/dL	anti CL IgG Ab	<8
Coagulation		Na	136 mmol/L (138-145)	sIL-2R	26400 U/mL (122-496)
PT (%)	93.40%	K	3.7 mmol/L	IFN-γ	105 U/mL
PT INR	1.04	Cl	101 mmol/L	IL-6	9.4 pg/mL
APTT	38.1 sec (25-38)	CRP	3.88 mg/dL (<0.14)	TNF-α	5.09 pg/mL
Fibrinogen	330 mg/dL	glucose	110 mg/dL		
D-dimer	1.4 μg/mL (<1.0)	Serum Iron	94 μg/dL	**EBV DNA load in PB**	
FDP	2.93 μg/mL (<5)	ferritin	16009 ng/mL (10-80)	EBV-PCR	5.2×10^5 copies/mL

PT: prothrombin, APTT: activate partial thromboplastin time, FDP: fibrin degradation products, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, γ-GTP: gamma-glutamyl transferase, TP: total protein, Alb: albumin, BUN: blood urea nitrogen, Cr: creatinine, Na: sodium, K: potassium, Cl: chlorine, CRP: C-reactive protein, EBV: Epstein-Barr virus, VCA: virus capsid antigen, Ig: immunoglobulin, EBNA: EBV nuclear antigen, CMV: cytomegalovirus, ANA: anti-nuclear antibody, PR3: proteinase 3, ANCA: anti neutrophil cytoplasmic antibody, MPO: myeloperoxidase, CL: cardiolipin, β2GP1: β2-glycoprotein 1, sIL-2R: soluble interleukin-2 receptor, IFN: Interferon, IL-6: interleukin-6, TNF: tumor necrosis factor, DNA: deoxyribonucleic acid, PB: peripheral blood, PCR: polymerase chain reaction. Parentheses indicate normal ranges.

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