

Case Report

Acute multiple organ dysfunction caused by Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in adults: a case report and literature review

Fu Su*, Rongshui Yang*, Chao Ma, Guoqiang Chen, Meiling Huang, Weixing Wang, Xinhui Su

Department of Nuclear Medicine, Zhongshan Hospital, Xiamen University, Xiamen 361004, China. *Equal contributors.

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Abstract: Background: Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH) is the most frequent subtype of secondary HLH that is more commonly observed in adults with poor outcome. Multiple organ damage in HLH has only been demonstrated in a limited number of patients. However, EBV-HLH presenting as acute three organ dysfunctions (respiratory dysfunction, liver dysfunction and cardiac dysfunction) has rarely been described in adult patients. Case summary: A 64-year-old female was admitted to our hospital with a 10-day history of fever accompanied with asthma and cough for last 2 days. At admission, she had acute three organ dysfunction with unknown etiology. The laboratory data revealed that she had thrombocytopenia, anemia, hyperferritinemia, hypertriglyceridemia, elevated levels of lactic dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and hypofibrinogenemia. Real-time PCR detected a high copy number of EBV DNA in the peripheral blood mononuclear cells (PBMCs). The primers for amplifying the EBV DNA sequences were as follows: forward, CGGAAGCCCTCTGGACTTC, and reverse, CCCTGTTTATCCGATGGAATG. Finally, a bone marrow biopsy revealed hemophagocytic cells, and she was diagnosed with EBV-HLH. Based on HLH-2004 criteria and her liver dysfunction, the patient was treated with 75% dose-reduced etoposide, prednisolone and supportive treatments. Her condition started improving after one week, and her abnormal laboratory findings decreased near to or within normal ranges at day 14. Her clinical signs and symptoms were resolved completely during 3 months follow-up after hospital discharge. Conclusions: Acute multiple organ injuries in adult patients with EBV-HLH have received increasing attention. EBV-HLH should be considered in the patients with acute multiple organ dysfunctions of indeterminate cause when there is remarkable high copy number of EBV DNA in PBMCs. EBV-HLH is a hyper-inflammatory syndrome with high mortality. Early diagnosis and prompt treatment should therefore be emphasized. Furthermore, it is also suggested that an optimized comprehensive therapeutic regimen based on etoposide and corticosteroids might have been beneficial for the patient's survival.

Keywords: Acute multiple organ dysfunctions, Epstein-Barr virus, infection, hemophagocytic lymphohistiocytosis

Introduction

Hemophagocytic lymphohistiocytosis (HLH), previously known as macrophage activation syndrome, was first reported by Scott and Robb-Smith in 1939 [1]. It is divided into two categories based on its etiology: primary and secondary (acquired) HLH. Primary HLH is an autosomal recessive genetic disease, whereas secondary HLH is often associated with and caused by viral infections, malignant tumors, and autoimmune diseases. Among these triggering

conditions, infection is the main trigger factor, constituting 50.4% of secondary HLH [2]. Epstein-Barr virus (EBV) is the most common infectious agent in the patients with viral-associated HLH [2].

The epidemiology of Epstein-Barr virus associated HLH (EBV-HLH) remains unclear at present. EBV-HLH that occurs in adult patients living in Asian countries accounts for approximately 40% of patients with HLH in Japan and Korea, and 75% in China [3]. EBV is a lymphotropic

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human gamma-1 herpesvirus that is transmitted primarily through saliva via the oropharyngeal route. Primary EBV infection is mostly asymptomatic, following persistent infection. EBV can infect not only B cells but also T and NK cells. EBV-infected T and/or NK cells might induce the accumulation and proliferation of hemophagocytic macrophages that cause hypercytokinemia and damage various cells and tissues [1, 4]. The pathophysiological mechanism for EBV-HLH is that the abnormal immune response caused by EBV infection leads to hyper-cytokinemia, which causes multiple organ and tissue damage [5]. HLH presents with a wide spectrum of clinical manifestations that are non-specific with generally acute or sub-acute (1-4 weeks) clinical presentation [6]. Patients with HLH typically present with continuous high fever ($> 38.5^{\circ}\text{C}$), hepatosplenomegaly, cytopenia, coagulation abnormalities, and fatal multiple organ failure. Since its clinical and laboratory features are similar to some diseases, such as sepsis, autoimmune diseases, viral infections, and malignancy, the diagnosis of HLH, especially in adults is the most challenging aspect of the disease that results in delayed recognition and treatment of rapidly progressive multiple organ dysfunction/failure [7]. Herein is presented a case with acute three organ dysfunctions (acute respiratory dysfunction, liver dysfunction and cardiac dysfunction) caused by EBV-HLH, with a view to improving the early diagnosis and prompt treatment of this kind of acute multiple organ dysfunctions.

Case report

A 64 year old female who presented with a 10-day history of fever accompanied by asthma and cough for last 2 days was admitted to the Hematology Medicine Intensive Care Unit (ICU), and rapidly progressed to acute three organ dysfunctions that were characterized by respiratory, liver, and cardiac dysfunction.

At the onset of disease, she had hyperthermia (a peak temperature of up to 39.5°C) for 10 days. The patient was treated for influenza at a local clinic for 7 days with minimal improvement. She also had unremarkable medical history including liver disease, cancer, and tuberculosis, and was not known to be an alcoholic and smoker.

On physical examination, at the time of admission, she had enlarged liver and spleen (sized 2

cm and 3 cm, respectively), palpable below the costal margin. Pulmonary auscultation revealed symmetrical respiratory sounds with bilateral crackles. Other superficial lymph nodes were not palpable except for those in the bilateral axilla (measured 2.0 cm in diameter). She had no obviously jaundice over the entire body. Neither spider telangiectasis nor palmar erythema was noted. The remainder of the physical examination was unremarkable. Chest plain computed tomography (CT) scan showed ill-defined ground-glass opacities in bilateral lower lung lobes. Ultrasound revealed multiple enlarged lymph nodes in the bilateral axilla (largest one was 3.0 cm length \times 2.5 cm width), heterogeneous liver echogenicity and splenomegaly (measured 13.7) with no focal lesions. In addition, she had a low QRS voltage at the chest lead electrocardiogram, and abnormal echocardiography findings such as enlarged left atrium and left ventricle, reduced left ventricular global and regional activations (**Figure 1, Table 2**). Abdominal/pelvic plain CT showed an enlarged spleen and no further abnormalities. Blood hematology and biochemistry were significant for thrombocytopenia, anemia, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, and elevated cardiac and liver markers. The laboratory findings for the patient at the time of admission are shown in **Table 1**. Arterial blood gas analysis was also abnormal (**Table 1**). Real-time PCR detected high copy number of EBV DNA (7.31×10^4 copies/ μg DNA) in the peripheral blood mononuclear cells (PBMCs) at the time of hospital admission. The primers for amplifying the EBV DNA sequences were as follows: forward, CGGAAGCCCTCTGGACTTC, and reverse, CCCTGTTTATCCGATGGAA-TG. Immunofluorescence assays revealed high titer of EBV-VCA-IgG (825.6 RU/mL, normal range: 0-16 RU/mL), positive for EBV-VCA-IgA and EBV-ED/D-IgA, whereas the assays were negative for EBV-VCA-IgM. Additional, viral assays were negative for human immunodeficiency virus, hepatitis B virus and hepatitis C. Blood and urine cultures showed no growth. Tests for antinuclear antibody, double-stranded DNA antibody, anticyclic peptide containing citrulline, immunoglobulin A (IgA), IgG, IgM, and serum complement C3, C4, were also negative.

The patient was diagnosed with acute three organ dysfunctions (acute respiratory dysfunction, liver dysfunction and cardiac dysfunction)

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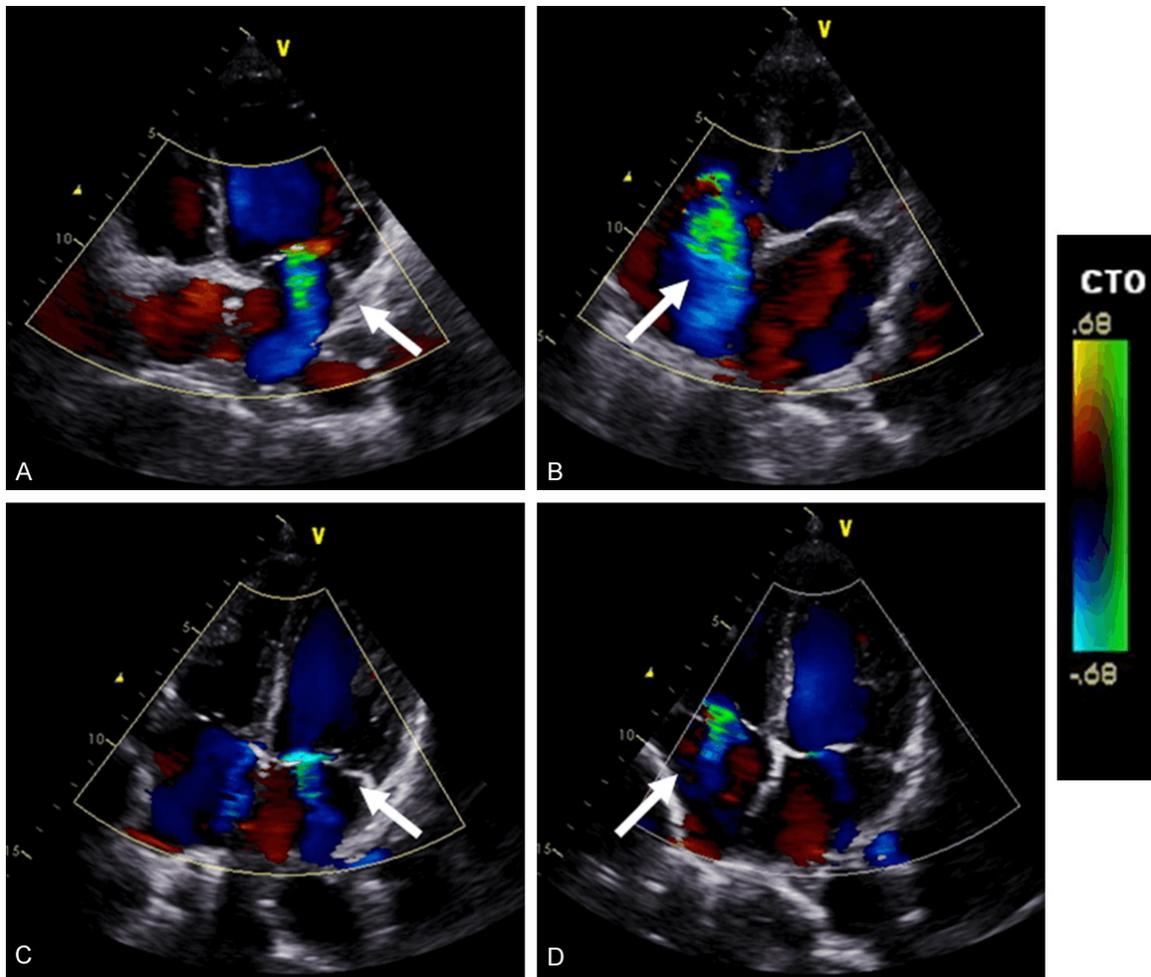


Figure 1. Echocardiography demonstrated changes of mitral and tricuspid regurgitation before and after treatment. (Before treatment, A: Moderate mitral regurgitation; B: Moderate tricuspid regurgitation. After treatment, C: Slight mitral regurgitation; D: Slight tricuspid regurgitation).

with unknown etiology at admission. Based on her clinical manifestations and laboratory findings, HLH was suspected. On 2 day after admission, a bone marrow puncture-biopsy was performed, and revealed an elevated percentage hemophagocytosis of 3.0% (normal range, 0) (**Figure 2**). The patient was then diagnosed as EBV-HLH with acute three organ dysfunctions accords with both HLH-2004 and HScore criteria [8, 9]. Her HScore was 278.

To establish a more efficacious treatment strategy, respiratory specialists, oncologists, hepatologists, and cardiologists were consulted from within the hospital. According to HLH-2004 criteria [8], because of her liver dysfunction, the patient was treated with 75% dose-reduced etoposide (112.5 mg/m²) twice a week (on day

4 and day 7) and prednisone (0.8 mg/kg/day, orally) for two weeks, followed by only prednisone (0.8 mg/kg/day, orally) from the third to the fourth week of hospitalization. Additional supportive treatments included mechanical ventilation support, liver-protective agents, cardiac agents, energy supplements and vitamins, intravenous infusion of plasma and albumin, and maintenance of water-electrolyte and acid-base equilibriums. After 1 week, the patient's condition started improving and she was weaned off the ventilator and her fever subsided. After 2 weeks, the patient continued with progressive clinical improvement and was transferred out of the ICU to the ward for further management. Her abnormal laboratory findings at the time of admission decreased near to or within normal ranges (**Tables 1, 2**). The patient

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Table 1. Trend of laboratory findings during the initial hospital stay

Parameters	Unit	Normal range	Results							
			1 d	3 d	7 d	10 d	14 d	18 d	21 d	28 d
Hematology										
WBC	10 ⁹ /L	3.50-9.50	4.85	5.10	4.52	4.76	6.21	7.31	6.85	5.78
INR	%	40.0-75.0	85.6	90.5	80.3	72.7	72.0	66.4	59.1	64.6
RBC	10 ¹² /L	3.80-5.10	3.00	2.81	3.32	3.51	4.01	4.34	4.25	4.65
HGB	g/L	115-150	84	90	98	94	102	112	134	145
PLT	10 ⁹ /L	125-350	35	46	76	82	97	143	169	232
Chemistry										
PT	sec	9.0-13.0	13.3	14.1	13.4	12.6	12.0	11.7	10.6	11.3
PTA	%	0.82-1.18	1.16	1.09	0.95	0.98	1.10	1.06	0.88	1.25
APTT	sec	20.0-40.0	44.1	46.6	50.5	38.7	36.2	30.7	28.0	33.7
Serum FIB	g/L	2.00-4.00	0.94	0.86	1.10	1.65	2.05	2.87	3.01	3.36
Serum ALT	U/L	7.0-40.0	73.0	77.1	70.5	65.1	53.1	44.6	32.1	30.2
Serum AST	U/L	13-35	96.0	84.8	77.0	70.3	63.9	44.5	34.3	22.6
Serum Tbil	μmol/L	3.40-17.10	23.30	22.92	24.51	20.19	17.13	11.35	12.40	8.76
Serum LDH	U/L	109.0-245.0	441.0	462.3	389.3	303.9	280.8	232.4	208.7	188.2
Serum ferritin	ng/L	13.0-150.0	3878.0	3567.4	3054.2	2797.5	1030.1	654.8	145.3	99.8
Serum triglycerides	mmol/L	0.00-1.70	4.68	5.01	3.78	2.02	1.89	1.60	1.34	0.55
Serum Cr	μmol/L	53.0-97.0	82.0	90.3	86.6	78.4	70.7	84.3	73.4	77.3
Serum BUN	mmol/L	2.90-8.20	5.58	6.09	7.22	6.93	7.34	5.98	6.30	6.55
Serum albumin	g/L	40.00-55.00	20.40	23.7	34.4	43.2	45.3	46.6	44.7	47.8
Serum CRP	mg/L	0.00-5.00	144.00	154.24	128.36	94.53	84.57	56.58	44.33	20.34
Serum D-dimer	mg/L	0.00-0.55	22.68	19.34	25.55	10.87	5.23	2.31	0.77	0.45
Serum CK	U/L	26.0-192.0	478.0	489.5	449.7	366.4	300.5	247.3	175.6	155.5
Serum HScTnT	μg/L	0-0.10	0.027	0.032	0.025	0.041	0.035	0.030	0.042	0.05
Serum NT-proBNP	ng/L	0-300.00	6809.0	6689.4	7045.7	5051.9	2156.5	674.4	263.2	277.6
Serum AAG	mg/L	500.00-1200	2500.0	2356.3	2303.7	1894.6	1543.6	1156.3	1067.6	905.8
EBV test										
EBV DNA in PBMCs	copies/μg	0	7.31 × 10 ⁴			5.64 × 10 ³		1.23 × 10 ²		0.44 × 10 ²
EBV-VCA-IgG	RU/mL	0-16	825.6							
EBV-VCA-IgA		negative	Positive							
EBV-ED/D-IgA		negative	Positive							
EBV-VCA-IgM		negative								
Arterial blood gas analysis										
pH		7.350-7.450	7.507	7.449	7.433	7.445	7.447	7.405	7.423	7.402
PO ₂	mmHg	80.0-100.0	49.5	96.8	98.7	98.6	98.4	98.7	98.8	98.5
PaCO ₂	mmHg	35.0-45.0	23.7	38.4	40.6	43.3	44.6	43.4	44.0	43.3
HCO ₃ ⁻	mmol/L	21.40-27.30	18.70	22.87	24.62	23.89	26.06	25.76	26.33	26.04
SO ₂	%	91.90-99.00	89.30	90.3	98.5	98.7	98.6	98.9	98.7	98.8

WBC = white blood cell count, INR = international normalized ratio, RBC = red blood cell count, HGB = hemoglobin, PLT = platelet count, PT = prothrombin time, PTA = prothrombin time activity, APTT = activated partial thromboplastin time, FIB = fibrinogen, ALT = alanine aminotransferase, AST = aspartate aminotransferase, Tbil = total bilirubin, LDH = lactate dehydrogenase, Cr = creatinine, BUN = blood urea nitrogen, CRP = C-reactive protein, NT-proBNP = N-terminal pro-brain natriuretic peptide, CK = creatine kinase, HScTnT = high sensitivity cardiac troponin T, AAG = α1-acid glycoprotein, PBMCs = peripheral blood mononuclear cells.

was then discharged home after 4 weeks on further steroid course for 2 weeks. Her clinical signs and symptoms were resolved completely during 3 months follow-up at discharge from the hospital.

The patient provided a written informed consent for the case report. The consent procedure was approved by the Ethics Committee of Zhongshan Hospital, Xiamen University.

Discussion

HLH has a high mortality rate, accounting for 22-59% of HLH patients [10]. Early diagnosis and prompt treatment are therefore critical and could be a key to prevention of fatal outcomes in HLH. HLH-2004 is the internationally accepted diagnostic criteria for HLH that has been widely used in clinical practice [8]. However, recent studies have shown that the HLH-2004

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Table 2. Echocardiography findings during the initial hospital stay

Parameters	Unit	Normal range	Results	
			1 d	25 d
RVOT	mm	< 30	30	28
AO	mm	20-35	26	29
LA	mm	19-35	43	40
RV	mm	< 20	22	23
AAO	mm	< 37	32	34
MPA	mm	< 28	27	25
IVS	mm	1-11	8.8	9.1
LVD	mm	35-55	58	55
LVS	mm	20-40	39	34
LVPWD	mm	1-11	7	9
EF	%	50-75	59	58
FS	%	25-50	32	31
TV	m/s	0.3-0.7	3.2	2.8
PPG	mmHg	< 30	42	31
PASP	mmHg	< 40	52	41
E/A		1.0-2.0	> 1.0	> 1.0
DT	ms	160-240	185	186
IVRT	ms	70-90	78	80

RVOT = right ventricular outflow track, AO = aortic bulb, LA = left atrium, RV = right ventricle, AAO = ascending aorta, MPA = main pulmonary artery, IVS = interventricular septum, LVD = left ventricle in diastole, LVS = left ventricle in systole, LVPWD = left ventricular posterior wall dimension, EF = ejection fraction, FS = fractional shortening, TV = three orifice velocity, PPG = peak pressure gradient, PASP = pulmonary artery systolic pressure, E/A = E peak/A peak, DT = E peak deceleration time, IVRT = isovolumic relaxation time.

diagnostic criteria do not apply easily for most cases of secondary HLH, because it is derived from the experience in pediatric patients with congenital HLH [11]. Highly elevated ferritin levels (> 10,000 ng/L) are thought to be 90% sensitive and 96% specific for HLH in pediatrics [12], but the same does not hold true for adults. Markedly elevated ferritin levels (> 50,000 ng/L) can be seen in a few other disorders, such as renal failure, hepatocellular injury, infections, and hematologic malignancies. Cattaneo C, et al. [11] reported that 35 patients with acquired HLH had hyperferritinemia, fever and splenomegaly according to HLH-2004 criteria, and these symptoms were present in more than 90% of patients, whereas other criteria were present in less than 70% of cases, while bone marrow hemophagocytosis was in 51% of cases only. Moreover biological markers NK cell activity or soluble CD25 were difficult to

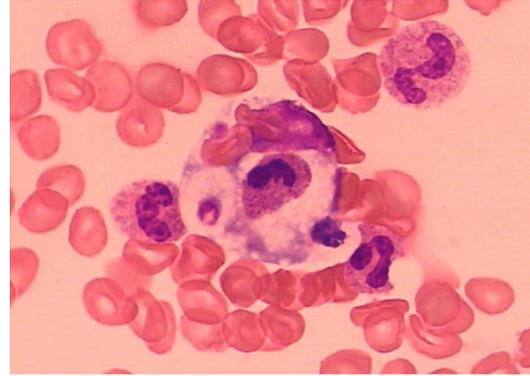


Figure 2. Bone marrow smear indicated hemophagocytic histiocytes by light microscopy on the second day after admission (before treatment) (Wright-Giemsa staining, $\times 100$).

be obtained timely, and NK cell activity was reduced in five of seven patients. Therefore, the HScore criteria have been proposed for adult patients with suspected acquired HLH in recent years [9, 11]. This HScore holds three clinical, five biological and one cytologic weighted variable. The best cut off value for the HScore was estimated at 169, corresponding to a sensitivity of 93% and specificity of 86% for acquired HLH in adults, with 90% of patients accurately classified [9]. In this patient, the HScore was calculated based on features on admission (algorithm available online <http://saintantoine.aphp.fr/score/>). The HScore was 278, corresponding to a 99.89% probability of having HLH.

In clinical practice, EBV-HLH in adults is often first classified as lymphomas [1]. However, it is easy to find morphologically malignant cells or malignant structures in the bone marrow or lymph nodes from patients with lymphomas. Importantly, use of an EBV-terminal probe and/or T-cell receptor gene rearrangement assays show that the bone marrow or lymph node lymphocytes in EBV-HLH cases are often mono- or oligo-clonal [1]. The diagnostic criteria for the EBV-HLH are that patient meets HLH diagnosis and EBV positive. This patient met the HLH-2004 diagnostic criteria, and had a high copy number of EBV DNA in the peripheral blood mononuclear cells (PBMCs), with high titer of EBV-VCA-IgG, and positivity for EBV-VCA-IgA and EBV-ED/D-IgA.

It has been shown that adults with EBV-HLH have worse prognosis than children with this

disease [1]. Two treatment guidelines for HLH, HLH-94 [13], and HLH-2004 [8], were developed based on the experience in children with primary HLH. They include dexamethasone, etoposide, cyclosporine, and intravenous immunoglobulin. These treatment methods have showed increased survival compared with historical controls [6]. Although no studies have investigated the efficacy of the protocols in adults with EBV-HLH, some studies demonstrated that therapeutic regimens containing etoposide provided survival benefit in adults with EBV-HLH [10, 14, 15]. The survival from early etoposide treatment in young adults with EBV-HLH is significantly better than that of the no/late etoposide treatment, suggesting that etoposide might act by partly blocking the EBV [14]. Risk and benefit of etoposide in this group of patients should be carefully evaluated, given that severe liver and renal dysfunctions are commonly encountered in HLH patients [7]. Interestingly, a retrospective study has revealed that 29 of 56 secondary HLH adult patients with multi-organ failure were successfully treated with reduced-dose etoposide with close monitoring [10]. Phenotypically, EBV-HLH is a heterogeneous disorder with various symptoms, ranging from mild to severe. Furthermore, the clinical course for EBV-HLH is diverse and can range from self-limiting in some patients to severe/aggressive and fatal in others [16]. Therefore, prompt and appropriate therapeutic strategy should be established based on the laboratory findings at the time of diagnosis. In our patient, she presented with mild multiple organ dysfunction (respiratory dysfunction, liver dysfunction and cardiac dysfunction), and dose-reduced etoposide was given along with steroid therapy in the first 2 weeks, combined with supportive therapy, which led to a striking improvement in the respiratory and liver function and clinical status of the patient. Kogawa K, et al. [17] reported that among several prognostic factors, patients with both hyperbilirubinemia (> 1.8 mg/dl) and hyperferritinemia ($> 20,300$ ng/ml) at the time of diagnosis had significantly poorer outcomes than those with low serum bilirubin and ferritin levels. In this case report, the patient had lower levels of hyperbilirubinemia (23.3 μ mol/L = 1.36 mg/dl) and hyperferritinemia (3878 ng/ml), and had a better outcome.

In conclusion, acute multiple organ injury in adult patients with EBV-HLH have received

increasing attention. EBV-HLH should be considered in the patients with acute multiple organ dysfunction of indeterminate cause when there is remarkable high copy number of EBV DNA in PBMCs. EBV-HLH is a hyper-inflammatory syndrome with high mortality, so, early diagnosis and prompt treatment should be emphasized. Finally, an optimized comprehensive therapeutic regimen based on etoposide and corticosteroids might have been beneficial for the patient's survival.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xinhui Su, Department of Nuclear Medicine, Zhongshan Hospital, Xiamen University, No. 201 Hubin South Road, Xiamen 361004, China. Tel: 86-592-2292536; Fax: 86-592-2993352; E-mail: suxinhui@163.com

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