【 CASE REPORT 】

Successful Treatment of Herpes Simplex Virus (HSV)-1-associated Hemophagocytic Lymphohistiocytosis (HLH) with Acyclovir: A Case Report and Literature Review

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Abstract:

Hemophagocytic lymphohistiocytosis (HLH) associated with herpes simplex virus (HSV)-1 infection (HSV-1-HLH) is uncommon and is potentially fatal without appropriate treatment. We herein report the case of an adult patient with HSV-1-HLH who was successfully treated with acyclovir. A 69-year-old man developed fever, pancytopenia and liver enzyme elevation after the resolution of pneumonia. These findings and the presence of hemophagocytosis in the patient's bone marrow were consistent with a diagnosis of HLH. The patient was diagnosed with HSV-1-HLH based on the results of a polymerase chain reaction (PCR) for HSV-1. The early administration of acyclovir improved his clinical symptoms and laboratory results within two weeks. In the present case, the rapid and precise diagnosis facilitated the successful treatment of HSV-1-HLH.

Key words: hemophagocytic lymphohistiocytosis, herpes simplex virus-1, acyclovir

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a progressive, occasionally life-threatening disorder that is characterized by uncontrolled immune system activation (1). HLH was first described in 1939 by Scott (2). It is now classified as either primary (familial) or secondary (acquired). Primary HLH is caused by the dysregulation of cytotoxic T cells due to genetic mutations (3), whereas secondary HLH is induced by pathogens, neoplasms, autoimmunity and hypersensitivity to drugs; its exact mechanism has not been fully elucidated (4). It is generally thought that these triggers induce an abnormal release of cytokines, resulting in the proliferation of activated histiocytes with hemophagocytosis. Patients with HLH are at high risk of mortality (5). Viral infection, especially herpes group infection, is the most common in-

ducer of secondary HLH (1). Secondary HLH due to herpes simplex virus (HSV)-1 (HSV-1-HLH) is unusual and is associated with a high rate of mortality in cases in which the treatment is not initiated in the early stage of the disease (6). We herein describe a case of HSV-1-HLH that was promptly cured by acyclovir without immunosuppressive therapy.

Case Report

A 69-year-old Japanese man was admitted to our hospital in September 2015 with dyspnea and fever. The patient's history included essential hypertension, which had been treated with amlodipine for approximately 10 years. He had no episodes of recurrent infection. A complete blood count revealed mild anemia but was otherwise normal (white blood cell, $6.0 \times 10^3/\mu L$; hemoglobin, 11.0 g/dL; platelet, 14.0

Table 1. Laboratory Data at the Time of Diagnosis of HLH.

Complete blood counts		Biochemistry		RF	3 IU/mL
WBC	600 /μL	TP	5.1 g/dL	ANA	(-)
Neu	46.0%	Alb	3.0 g/dL	anti-dsDNA Ab	(-)
Lym	46.0%	AST	1,398 U/L	Virus Markers	
Mono	6.0%	ALT	379 U/L	HBs Ag	0.0 IU/mL
Aty-lym	2.0%	LDH	1,345 U/L	HBs Ab	0.0 mIU/mL
RBC	386×10⁴/μL	T-bil	0.7 mg/dL	IgM-HBcAb	(-)
Hb	11.5 g/dL	BUN	11.4 mg/dL	HCVAb	0.1 S/CO
Plt	8.9×10⁴/μL	Cre	0.56 mg/dL	HIV1/2Ab	0.1 S/CO
Coagulation tests		Na	131 mEq/L	CMV-IgM	(-)
PT-INR	1.63	K	3.8 mEq/L	CMV-IgG	(+)
APTT	54.7 s	CRP	9.78 mg/dL	EBV-VCA IgM	(-)
Fib	523 mg/dL	sIL-2R	1,295 U/mL	EBV-VCA IgG	(+)
D-dimer	4.79 μg/mL	ferritin	40,340 ng/mL	EBV-EBNA	(+)

WBC: white blood cells, Neu: neutrophils, Lym: lymphocytes, Mono: monocytes, Aty-lym: Atypical lymphocytes, RBC: Red blood cells, Hb: hemoglobin, Plt: platelet, PT: prothrombin time, APTT: activated partial thromboplastin time, Fib: fibrinogen, TP: total protein, Alb: albumin, AST: asparate aminotranferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, T-bil: total bilirubin, BUN: blood urea nitrogen, Cre: creatinine, CRP: C-reactive protein, sIL-2R: soluble interleukin-2 receptor, RF: rheumatoid factor, ANA: antinuclear antibodies, dsDNA: double strand DNA, Ab: antibody, Ag: antigen, HB: hepatitis B virus, HCV: hepatitis C virus, HIV: human immunodeficiency virus, CMV: cytomegalovirus, EBV: Epstein-Barr virus, VCA: viral capsid antigen, EBNA: EBV nuclear antigen
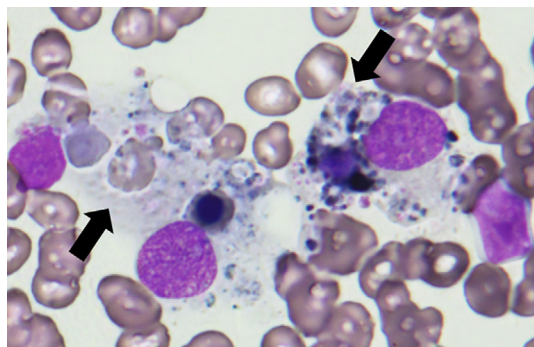

Figure 1. Bone marrow aspiration was performed six days after the recurrent fever. The bone marrow smear revealed a high number of activated macrophages with hemophagocytosis signs; the engulfment of red blood cells and platelets by an activated histiocyte can be seen (black arrow).

×10⁴/μL). The patient's liver and renal function were within the normal limits, while his ferritin level was slightly increased (746 ng/mL). Computed tomography (CT) on admission showed air space consolidation in the lower lobes of both lungs. He was diagnosed with aspiration pneumonia based on these findings. The causal pathogen was not identified by blood and sputum culturing or serological examinations. His clinical symptoms and imaging findings improved after the 7-day administration of piperacillin/tazobactam. However, he became febrile again three days after the resolution of pneumonia, with no sign of recurrent pneumonia. He remained febrile, with a body temperature of >38.5℃. Neutropenia and thrombocytopenia developed rapidly in the 6 days after the onset of the second fever. With the exception of blisters on the posterior pharyngeal wall, which were

suggestive of viral infection, there were no significant physical signs. The laboratory findings showed thrombocytopenia, neutropenia, elevated liver enzymes, an increased lactate dehydrogenase (LDH) level, and hyperferritinemia (Table 1). A bone marrow examination showed hypocellular marrow with histiocytic hyperplasia (macrophages, 15.0%) and hemophagocytic macrophage infiltration (Fig. 1). Abdominal ultrasonography and CT showed moderate splenomegaly without liver enlargement. Thus, the patient was diagnosed with HLH, as five of the eight diagnostic criteria in HLH-2004 (7) were fulfilled: fever, splenomegaly, cytopenias affecting at least two of three lineages in the peripheral blood, hemophagocytosis in the bone marrow, and hyperferritinemia. Based on the acute clinical course, we suspected that the patient's HLH had an infectious etiology. There was no evidence of either bacterial or fungal infections in repeated blood and urine cultures or serological examinations. We performed a multiplex polymerase chain reaction (PCR) to detect the genomic DNA of 12 viruses: HSV-1, HSV-2, varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes virus (HHV)-6, HHV-7, HHV-8, parvovirus B19, BK virus, JC virus, and hepatitis B virus (HBV) (8, 9). Only HSV-1 DNA was detected in his serum, and the HSV-1 DNA level was calculated using a real-time quantitative PCR. The changes in the HSV-1 DNA content and HSV-specific IgM and IgG antibodies over the treatment period are shown in Fig. 2. These findings were consistent with acute primary HSV-1 infection. Thus, the final diagnosis was HLH caused by a primary disseminated HSV-1 infection.

The administration of acyclovir (30 mg/kg/day) was started on the seventh day after the onset of the second fe-
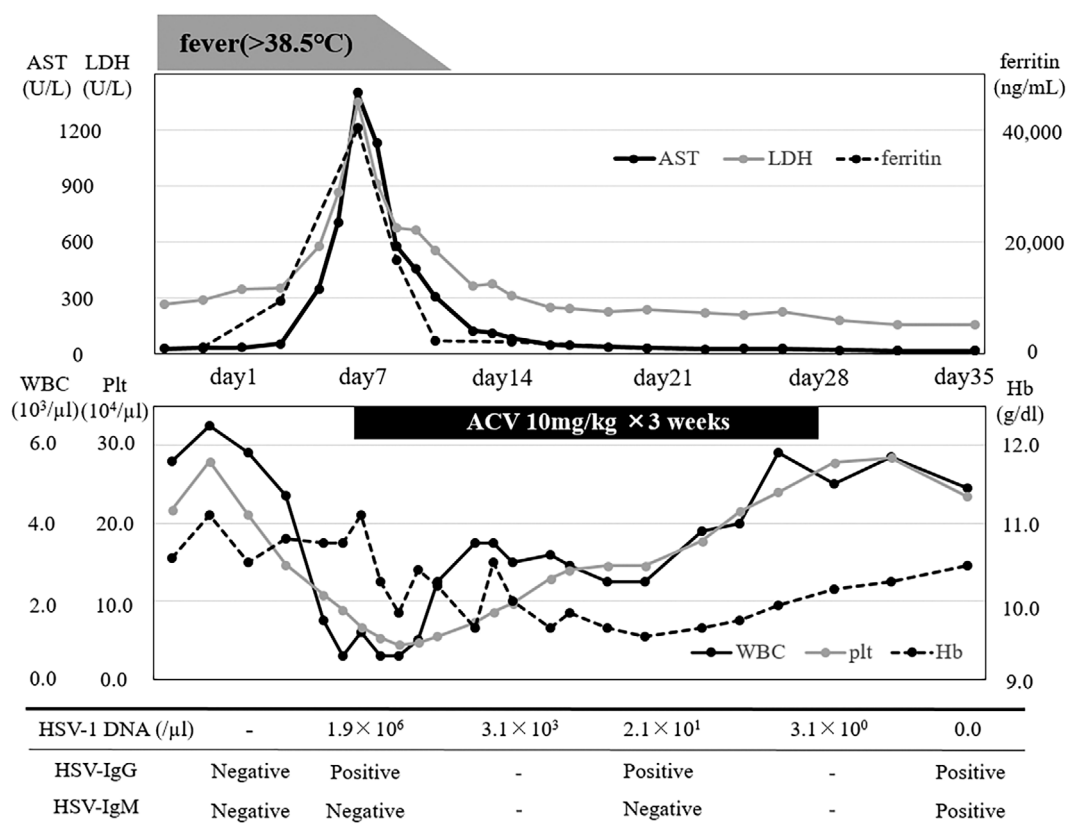
Figure 2. Clinical course of the present case. Sequential changes of the liver function, lactate dehydrogenase, ferritin and complete blood count during the treatment are shown. Day 1 is defined as the date when fever developed again after the improvement of pneumonia. HSV-1 DNA copy number and serological data of HSV-1 during the treatment are attached. ACV: acyclovir

ver. The serum levels of AST, ALT, and LDH decreased rapidly at just 3 days after the initiation of treatment and his temperature returned to normal after 2 more days. The severe pancytopenia and acute liver injury improved within 2 weeks after the initiation of treatment (Fig. 2). The reexamination of the patient's bone marrow showed normocellular marrow with a decreased number of macrophages (2.4%) and little hemophagocytic or macrophage infiltration. He was discharged in good general condition and no recurrence has been observed in the one year since treatment.

Discussion

We described the case of an elderly patient with secondary HLH caused by a primary disseminated HSV-1 infection that occurred after the treatment of pneumonia. The cause of secondary HLH should be carefully examined. First, we excluded causes associated with preceding pneumonia, since the patient's pneumonia had completely improved and the administration of antibiotics had finished when HLH was diagnosed. The imaging studies ruled out the presence of malignancies as a trigger of HLH. The absence of joint symptoms and normal levels of autoantibodies did not support a diagnosis of systemic autoimmune disease. The patient had no history of using medications that could cause HLH. Consequently, viral infection was the most

likely cause of HLH because there was no evidence of bacterial or fungal infection. PCR methods represent the most rapid and secure means of identifying a causal virus. We successfully identified HSV-1 as the cause of the patient's HLH using a multiplex PCR and diagnosed the patient with HSV-1-HLH.

Shimizu, et al. developed a multiplex PCR to detect all subtypes of herpes family viruses: HSV-1, HSV-2, VZV, EBV, CMV, HHV-6, HHV-7, and HHV-8 (7, 8). This method is useful for the screening of viral infections. In addition, the combination of a multiplex PCR and a quantitative real-time PCR permits the evaluation of therapeutic effects. Severe organ failure in secondary HLH is associated with poor outcomes. The rapid and accurate diagnosis of viral infections using a PCR might improve the prognosis of virus-associated HLH.

Ramos-Casals M et al. reviewed 2,197 cases of adult HLH collected from 677 previous reports (1). Viral infections (n=762, 35%) were the most frequent triggers of HLH. Herpes family viruses accounted for 62% of the cases of virus-associated HLH: EBV, 43%; CMV, 9%; and other herpes viruses, 10%. HLH caused by HSV (HSV-HLH) has mainly been reported in infected neonates and is rare in adults. Following a search of the PubMed database, 11 case reports on adult patients with HSV-HLH were found in the English literature: 4 were caused by HSV-1 (6, 10-12), 3

Table 2.   Clinical Data of Reported Cases of Adult HLH Associated with HSV-1 Infection.

Case (Refernce)	Age	Underlying diseases	Symptoms	Period from onset to treatment	Treatment	Outcome
Case 1 (12)	54	none	not excatly recorded	unrecorded	ACV, SPAD LT, steroids	unknown
Case 2 (6)	50	diabetes mellitus	fever, anorexia, mild dyspenea	8 days	ACV, steroids HD	death
Case 3 (11)	57	Wegener's granulomatosis	fever	not excatly recorded (approximately 2 weeks)	ACV, IVIG steroids etoposide	recovery (discharge after 13 weeks)
Case 4 (10)	52	none	fever, headache, arthromyalagia	6 days	ACV, IVIG etoposide	recovery (discharge after 4 weeks)
present case	69	none	fever	7 days	ACV	recovery (discharge after 4 weeks)

ACV: acylovir, IVIG: intravenous immunoglobulin, SPAD: single-pass albumin dialysis, LT: liver transplantaiton, HD: hemodialysis

were caused by HSV-2 (13-15), and the others were caused by unspecified subtypes (16-19). The four previous adult cases of HSV-1-HLH and our case are summarized in Table 2. Disseminated HSV-1 infection usually occurs in immunocompromised patients, but four of these five patients were immunocompetent. In case 1, acute liver failure and HLH induced by HSV-1 progressed despite antiviral treatment, and liver transplantation was performed after four days of intensive care. The transplantation was successful, but the long-term outcome was not described in detail (12). In case 2, the male patient had acute renal and liver failure on admission and died of HLH-related multi-organ failure after two days of intensive treatment (6). These 2 cases were treated with immunosuppressive therapy plus antiviral therapy. The other 3 patients without serious organ failure or coagulation abnormalities achieved a full recovery by treatment with acyclovir either with or without concurrent medications: intravenous immunoglobulin (IVIG), steroids, or etoposide. In case 4, only a few doses of etoposide were co-administered with acyclovir, resulting in good clinical condition for the patient. Our case was successfully treated with antiviral therapy and supportive care. In both cases, the clinical findings and laboratory data improved immediately after the initiation of antiviral therapy. Some patients with HSV-1-HLH may be curable by antiviral therapy alone without the use of immunosuppressive agents. Several previous studies have reported that patients recovered from secondary HLH, which was associated with infections such as tuberculosis, through the specific treatment of the underlying infection and supportive care alone (20, 21); however, immunosuppressive agents such as steroids and dexamethasone are considered to be indispensable from the initiation of treatment for EBV-associated HLH (EBV-HLH) (22). The treatment of HLH requires an individual approach that depends on the underlying trigger, disease severity, and clinical course.

In summary, a patient with HSV-1-HLH was treated successfully with antiviral therapy alone because we were able to make an early diagnosis and due to his less severe condi-

tion. The elimination of infectious triggers is an essential strategy for overcoming abnormal immune system activation in patients with secondary HLH. A rapid and precise diagnosis can contribute to the successful treatment of virus-associated HLH, including HSV-1. However, with the exception of EBV-HLH, there is little evidence regarding the significance of a combined approach with immunosuppressive therapy in viral-associated HLH. Further data and additional case studies will be required to establish the optimal treatments for virus-associated HLH.

The authors state that they have no Conflict of Interest (COI).

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