—Case Reports—

# Epstein-Barr Virus-Related Hemophagocytic Lymphohistiocytosis with Central Nervous System Symptoms

Masahiro Sakaguchi[1], Yasunobu Nagata[1], Yasuhiro Terasaki[2,3], Atsushi Takeyoshi[1], Shunichi Yasuda[1], Shunsuke Honma[1], Ryosuke Kinoshita[1], Atsushi Marumo[1], Toshio Asayama[1], Shunsuke Yui[1], Satoshi Wakita[1], Muneo Okamoto[1], Yusuke Kajimoto[2], Koichi Inokuchi[1] and Hiroki Yamaguchi[1]

[1]Department of Hematology, Nippon Medical School, Tokyo, Japan
[2]Department of Analytic Human Pathology, Nippon Medical School, Tokyo, Japan
[3]Division of Pathology, Nippon Medical School Hospital, Tokyo, Japan

Hemophagocytic lymphohistiocytosis (HLH) involves pathological histiocytes and phagocytosis of normal blood cells through activation of inflammatory cytokines. We report a case of Epstein-Barr virus-HLH in a 75-year-old woman who presented with fever, thrombocytopenia, and loss of consciousness. Epstein-Barr virus-HLH was diagnosed after we identified massive hemophagocytosis in bone marrow and Epstein-Barr virus DNA in cerebrospinal fluid. The HLH-2004 protocol was applied, and lactate dehydrogenase levels—which reflect HLH disease status—decreased. However, persistent loss of consciousness and multiple organ failure led to the patient's death on day 18. Most cases of primary and secondary HLH involve pediatric patients; adult cases are rare. Few cases of central nervous system involvement in older adults have been reported. Therefore, accumulation of more data will help in developing better treatment strategies. (J Nippon Med Sch 2023; 90: 126–134)

**Key words:** EBV-HLH, central nervous system infiltration

## Introduction

Hemophagocytic lymphohistiocytosis (HLH) involves pathological histiocytes and phagocytosis of blood cells via activation of inflammatory cytokines[1,2] and is classified as primary HLH (caused by congenital genetic abnormalities) and secondary HLH (triggered by infections or malignancies). Almost all cases of primary HLH are seen in pediatric patients. Secondary HLH is more common in adult patients and is caused by infection (30%), malignant tumors, and autoimmune diseases. Epstein-Barr virus (EBV) is responsible for 70% of infection-related HLH cases[3]. The clinical features of HLH include persistent high fever, splenomegaly, lymphadenopathy, hyperbilirubinemia, rash, and central nervous system (CNS) involvement (encephalopathy, meningism, and seizure). CNS involvement is rarer in adult HLH than in pediatric cases[4]. Previous reviews have not always distinguished between primary and secondary HLH; therefore, data on the frequency of CNS involvement in secondary HLH are sparse.

Among recent case studies of adults, the frequency of CNS involvement varies widely (10%-70%)[5], the number of cases is insufficient, and detailed information on clinical course is unavailable. Here, we report a case of EBV-HLH with CNS involvement in a 75-year-old woman.

## Case

Three months before presentation at our hospital, a 75-year-old woman had started therapy consisting of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP)[6] for EBV-positive diffuse large B cell lymphoma (DLBCL), not otherwise specified (stage III) (**Fig. 1**). The soluble interleukin-2 receptor (sIL-2R) level at this point was 961 IU/mL. After four R-CHOP cycles, she was in complete remission: computed tomography (CT) findings showed no residual evidence

Correspondence to Yasunobu Nagata, MD, PhD, Department of Hematology, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan
E-mail: y-nagata@nms.ac.jp
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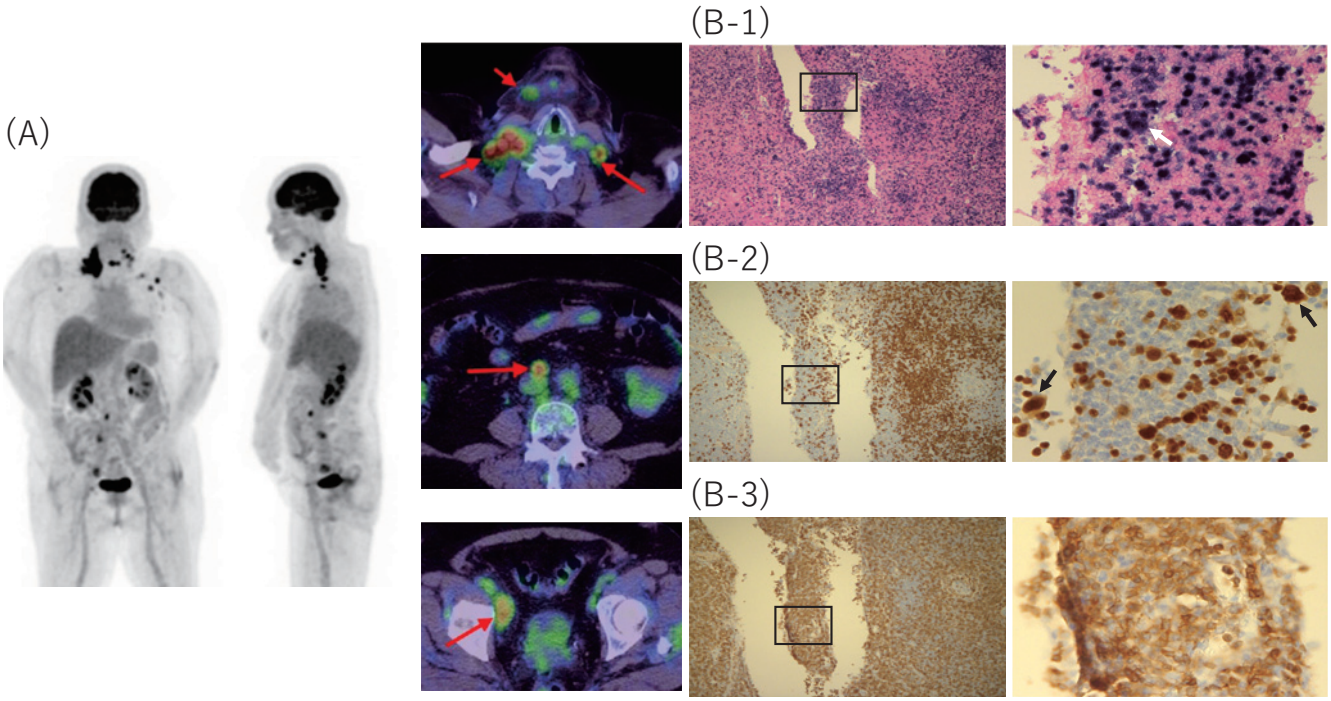


Fig. 1 Examination results at onset of Epstein–Barr virus (EBV)-diffuse large B cell lymphoma.
(A) Positron emission tomography findings: bilateral cervical, bilateral axillary, abdominal periarterial, and bilateral inguinal lymphadenopathy (compatible with stage III of the Ann Arbor staging classification).
(B) Pathological analysis of formalin-fixed paraffin-embedded specimens obtained from the right cervical lymph nodes. Representative images depicting labeling for EBV-encoded small RNA (EBER) (1) by in situ hybridization and PAX5 (2) or CD3 (3) by immunohistochemistry. In each row, the image on the right is an enlarged version of the rectangle in the image on the left. The white arrow indicates EBV-encoded small RNA-positive large tumor cells. The black arrows indicate PAX5-positive large tumor cells. EBV-infected large tumor cells are PAX5-positive B cells. T cells in the background are also enriched, which suggests that EBV can also infect T cells.

of DLBCL and sIL-2R level was controlled (516 IU/mL). However, her anorexia progressed and her performance status was worse at 4 days after starting R-CHOP therapy. She was admitted to hospital with loss of consciousness (LOC) on day 10 after chemotherapy. Lymphadenopathy identified at initial diagnosis had shrunk; however, hepatosplenomegaly, which was not observed at onset, was present.

Her body temperature was 37.1°C (increasing to 40.0°C immediately after admission), and consciousness level was E4V4M6 on the Glasgow Coma Scale. No obvious acute cerebral infarction or encephalitis was found on magnetic resonance imaging (MRI). Serum ferritin levels were elevated (**Table 1**), and a bone marrow examination on day 2 after admission revealed hemophagocytic macrophages (**Fig. 2**). In accordance with HLH-2004 diagnostic criteria[7], HLH was diagnosed. We considered the possibility of re-exacerbation of EBV-DLBCL; although treatment of DLBCL was considered effective, the new occurrence of hepatosplenomegaly made it difficult to distinguish whether the cause of LOC was HLH or rapid exacerbation of lymphoma. LOC could have been caused by CNS involvement in EBV-DLBCL.

Dexamethasone was administered on day 1 (**Fig. 3**; **Supplementary Fig. 1** (http://doi.org/10.1272/jnms.JNMS.2023_90-105)). Nevertheless, hepatic and renal function worsened, and intensive care, including mechanical ventilation and continuous hemodiafiltration, was essential. To treat complicated disseminated intravascular coagulation, blood transfusions (red blood cells, platelets, and fresh frozen plasma) and recombinant soluble human thrombomodulin were administered. Because of the proven efficacy of the combination of dexamethasone and etoposide in HLH-94 and HLH-2004 protocols for HLH[8–10], dexamethasone (20 mg/body) was administered on day 1 of illness, and etoposide was administered on day 3 (the dose was reduced by 50% because of marked hepatic dysfunction[2,11]).

In this study, two possibilities were assumed: (A) refractory HLH did not respond to steroid administration alone, and (B) DLBCL that had previously responded to chemotherapy may have developed resistance to treat-

Table 1 Laboratory findings

| On administration | | Biochemistry | | During treatment | |
|---|---|---|---|---|---|
| Blood count | | T-Protein | 6.9 g/dL | sIL-2r | 13,438 U/mL |
| WBC | 4,300 /μL | Alb | 3.6 g/dL | TG | 278 mg/dL |
| Stab | 24.5 % | BUN | 35.5 mg/dL | Ferritin | 129,480 ng/mL |
| Seg | 61.0 % | Cr | 1.47 mg/dL | Antinuclear antibody | <40× |
| Lym | 2.5 % | UA | 9.3 mg/dL | Direct Coombs | negative |
| Mono | 2.0 % | Na | 136 mmol/L | ADAMTS13 activity | 0.30 IU/mL |
| Eosino | 0.0 % | K | 5.0 mmol/L | TCR rearrangement (PB) | negative |
| Baso | 0.0 % | Cl | 99 mmol/L | HTLV-1 Ab | negative |
| Myelo | 3.5 % | Ca | 9.0 mg/dL | EBV, CMV antigenemia (C10/11) | negative |
| Metamyelo | 6.5 % | T-Bil | 1.06 mg/dL | EBV-DNA (serum) | $2.0\times10^7$ copies/mL |
| RBC | $421\times10^4$ /μL | D-Bil | 0.60 mg/dL | EBV-DNA (CSF) | $3.0\times10^3$ copies/mL |
| Hb | 12.2 g/dL | AST | 595 U/L | HSV-DNA (CSF) | $<2.0\times10^2$ copies/mL |
| Hct | 36.4 % | ALT | 301 U/L | VZV-DNA (CSF) | $<2.0\times10^2$ copies/mL |
| Plt | $6.1\times10^4$ /μL | LDH | 3,455 U/L | | |
| | | ALP | 421 U/L | Blood culture | negative |
| Coaguration | | γ-GTP | 190 U/L | CSF | |
| PT | 14.7 sec | CK | 812 U/L | cell | <1 /μL |
| PT-INR | 1.16 | BS | 365 mg/dL | protein | 69 mg/dL |
| APTT | 30.6 sec | CRP | 7.14 mg/dL | glucose | 79 mg/dL |
| Fib | 289 mg/dL | $NH_3$ | 56 μg/dL | Cl | 127 mmol/L |
| D-dimer | 30 μg/dL | | | LDH | 40 U/L |

Abbreviation, Stab; Stab cell, Seg; Segmented cell, Lym; Lymphocyte, Mono; Monocyte, Eosino; Eosinocyte, Baso; Basocyte, Myelo; Myelocyte, Metamyelo; Metamyelocyte, sIL-2r; soluble interleukin-2 receptor, TCR; T cell receptor, PB; Peripheral blood, HTLV-1; Human T-cell Leukemia Virus Type 1, CMV; Cytomegalovirus, EBV; Epstein-Barr virus, HSV; Herpes simplex virus, VZV; Varicella zoster virus, CSF; Cerebrospinal fluid.

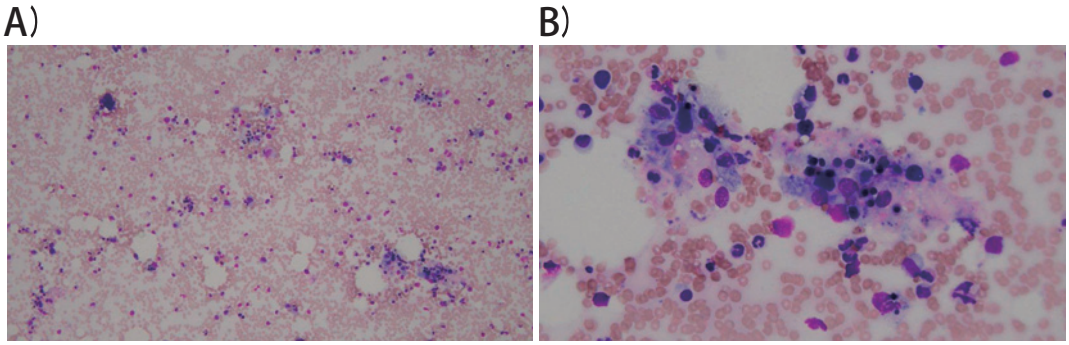


Fig. 2 Bone marrow aspiration images on day 2 after Epstein–Barr virus-hemophagocytic lymphohistiocytosis.
Left: objective, 40×.
Right: objective, 400×.

ment and led to rapid worsening of disease. Treatments effective for both HLH and DLBCL were necessary. At this point, the result of an EBV DNA test was unavailable; however, the background of the patient regarding EBV-DLBCL treatment suggested she might be in a state of EBV viremia, and EBV-HLH was also suspected.

Rituximab, reported to be effective against EBV-HLH, was added on day 4[12]. Methylprednisolone (1,000 mg/day) was administered for 3 days. Lactate dehydrogenase levels continued to increase. Increasing numbers of EBV DNA copies in peripheral blood (PB) ($2.0 \times 10^7$ copies/mL) and cerebrospinal fluid (CSF) ($3.0 \times 10^3$ copies/mL) were identified on day 8. These results suggested that EBV-HLH was the more likely diagnosis. The absence of an increase in the number of cells in CSF or malignant cells on cytopathology revealed that there was no CNS involvement from DLBCL. We concluded that all symptoms were due to EBV-HLH. Therefore, cyclosporine was administered on day 8. Although the lactate dehydrogenase level decreased, she did not recover consciousness.

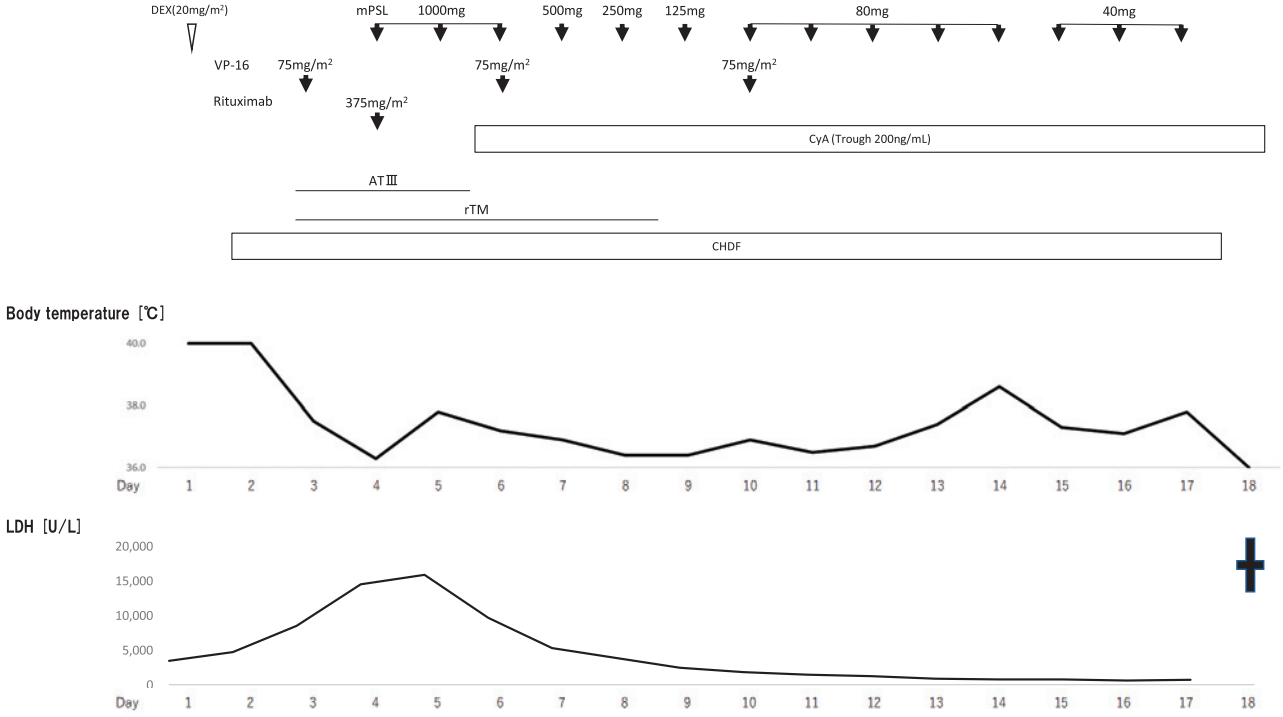


Fig. 3 Clinical course and laboratory data for Epstein–Barr virus-hemophagocytic lymphohistiocytosis.
LDH, lactate dehydrogenase; DEX, dexamethasone; CHDF, continuous hemodiafiltration; CyA, cyclosporine; AT, antithrombin; rTM, recombinant thrombomodulin; VP-16, etoposide; mPSL, methylprednisolone.

Anisocoria occurred on day 15, and CT examination revealed multiple cerebral infarctions, possibly caused by (i) cardiogenic cerebral embolism (atrial fibrillation started on day 7), (ii) embolism due to vegetation triggered by febrile neutropenia (the blood culture result was negative), or (iii) tumor embolism. However, we were unable to determine the cause of these multiple cerebral infarctions.

Because improvement of her general condition was unlikely, continuous hemodiafiltration was stopped, multiple organ failure progressed, and the patient died on day 18. A pathological autopsy was not performed.

## Discussion

When diagnosing HLH with CNS symptoms, other possibilities, including infectious (bacterial, viral, or fungal), autoimmune, and vascular diseases, should be considered. Physical examination and imaging (CT/MRI) findings and CSF and electroencephalogram tests are helpful. Gratton et al. reported that a cytokine storm caused by EBV infection led to blood cell phagocytosis through activation of macrophages and disruption of the blood-brain barrier, resulting in CNS dysfunction[13]. However, the mechanisms underlying the effects of hypercytokinemia on HLH-induced CNS symptoms remain unclear. There are few detailed reports of adult HLH cases with CNS symptoms, and only limited information, such as age and sex, is available for such patients. We collected and summarized detailed clinical information (**Table 2**)[13,14]. Thirty-six patients with HLH and CNS syndromes were identified. CSF data were available for 25 cases, and no increase in the number of CSF cells was observed in 48% (12/25). Of the 32 cases for which imaging results were available, 31% (10/31) showed no abnormalities on head MRI or CT, even though they exhibited CNS symptoms. Klein et al. stated that it is difficult to distinguish between EBV meningoencephalitis and HLH as a cause of CNS symptoms[5]. The patients described in **Table 2** did not undergo detailed examination regarding the cause of consciousness disturbance, which we assumed would be difficult to determine. The representative clinical course of the present patient was consistent with a diagnosis of EBV-HLH with CNS symptoms.

EBV reactivation or progression of DLBCL was considered the cause of HLH in the present case, and it was difficult to distinguish between them. It is unclear whether EBV viremia was present at the early onset of EBV-positive DLBCL. EBV infection in B cells was confirmed by histopathological examination at the time of early onset, and although there was no evidence to deny

Table 2 Review of CNS symptoms due to HLH

| Age | Sex | Underlying condition | Neurological symptoms | CSF | CT/MRI findings | Studies |
|---|---|---|---|---|---|---|
| 17 | F | EBV-VAHS | Limb paralysis, cranial nerve palsies | P: 180 mm$H_2O$, L: 6×$10^6$/L, Pro: 46 mg/dL | MRI: focal lesion in temporal lobe, without enhancement; meningeal enhancement | 14 |
| 17 | M | EBV-VAHS | Seizures | NA | w.n.l. | 14 |
| 20 | F | EBV-VAHS | Seizures, irritability | NA | NA | 14 |
| 20 | M | CMV-VAHS, HHV6-VAHS | Headache | P: 268 mm$H_2O$, L: 0×$10^6$/L, Pro: 21 mg/dL | MRI: focal lesion in frontal lobe, without irregular enhancement | 14 |
| 21 | F | NA | Encephalopathy, seizures/status epilepticus | L: 43×$10^6$/L, Pro: 1,206 mg/dL | Confluent cortical and subcortical T2 hyperintensity with petechial hemorrhage, scattered white matter T2 hyperintensities, symmetric T2 hyperintensity in the basal ganglia and external capsule, leptomeningeal enhancement | 13 |
| 23 | F | EBV-VAHS, Lymphoma | Seizures | P: 130 mm$H_2O$, L: 0×$10^6$/L, Pro: 30 mg/dL | MRI: Meningeal enhancement | 14 |
| 24 | F | EBV-VAHS | Headache; disturbance of consciousness | NA | CT: hemorrhage | 14 |
| 26 | M | EBV-VAHS | Disturbance of consciousness | P: 190 mm$H_2O$, L: 0×$10^6$/L, Pro: 30.8 mg/dL | w.n.l. | 14 |
| 28 | F | EBV-VAHS | Cranial nerve palsies, limb paralysis | NA | MRI: focal lesions in frontal lobe and basal ganglia, without enhancement | 14 |
| 28 | M | EBV-VAHS | Seizures | P: 200 mm$H_2O$, L: 3×$10^6$/L, Pro: 144 mg/dL | MRI: diffuse white matter signal changes | 14 |
| 29 | F | NA | Disturbance of consciousness, irritability, limb paralysis | P: 150 mm$H_2O$, L: 0×$10^6$/L, Pro: 32 mg/dL | w.n.l. | 14 |
| 30 | M | HHV-7-VAHS | Disturbance of consciousness | P: 190 mm$H_2O$, L: 1×$10^6$/L, Pro: 65 mg/dL | MRI: focal lesions in cortical, adjacent subcortical lesions and cerebellum | 14 |
| 31 | F | CMV-VAHS, HHV6-VAHS | Memory loss | P: 60 mm$H_2O$, L: 0×$10^6$/L, Pro: 72 mg/dL | MRI: focal lesions in cerebellum, with ring contrast-enhancement | 14 |
| 32 | M | EBV-VAHS | Irritability | P: 150 mm$H_2O$, L: 0×$10^6$/L, Pro: 32 mg/dL | w.n.l. | 14 |
| 33 | F | HSV-VAHS | Limb paralysis | P: 150 mm$H_2O$, L: 0×$10^6$/L, Pro: 29.3 mg/dL | CT: multiple hypodense foci | 14 |
| 36 | M | EBV-VAHS, lymphoma | Cranial nerve palsies, headache | P: 230 mm$H_2O$, L: 30×$10^6$/L, Pro: 165 mg/dL | MRI: focal lesions in parietal lobe, with nodular enhancement | 14 |
| 38 | M | EBV-VAHS | Encephalopathy, nystagmus, spastic tetraparesis, status epilepticus | L: 2×$10^6$/L, Pro: 147 mg/dL | MRI: Patchy T2 hyperintensities and nodular enhancement in the periventricular white matter and deep gray nuclei, scattered punctate foci of restricted diffusion | 13 |
| 42 | F | EBV-VAHS | Headache | P: 60 mm$H_2O$, L: 0×$10^6$/L, Pro: 26.2 mg/dL | w.n.l. | 14 |
| 44 | F | EBV-VAHS | Seizures, cranial nerve palsies, meningism | P: 145 mm$H_2O$, L: 0×$10^6$/L, Pro: 64 mg/dL | w.n.l. | 14 |
| 44 | F | EBV-VAHS | Encephalopathy, right hemiparesis | NA | Numerous foci of restricted diffusion within all of the supratentorial lobes and within the bilateral cerebellar lobes involving white and gray matter | 13 |
| 45 | M | EBV-VAHS | Seizures | P: 200 mm$H_2O$, L: 20×$10^6$/L, Pro: 140 mg/dL, EBV-DNA+ | MRI: focal lesion in occipital lobe, without enhancement | 14 |
| 49 | F | Lymphoma | Irritability | NA | NA | 14 |

Table 2 Review of CNS symptoms due to HLH (continued)

| Age | Sex | Underlying condition | Neurological symptoms | CSF | CT/MRI findings | Studies |
|---|---|---|---|---|---|---|
| 52 | M | EBV-VAHS | Headache; disturbance of consciousness | NA | MRI: focal lesion in basal ganglia, without enhancement | 14 |
| 52 | M | EBV-VAHS | Disturbance of consciousness | NA | NA | 14 |
| 53 | M | EBV-VAHS | Irritability, disturbance of consciousness | NA | NA | 14 |
| 54 | M | EBV-VAHS | Disorientation, inattention, perseverative speech, apractic gait | L: $7\times10^6$/L, Pro: 59 mg/dL | Multiple confluent white matter T2 hyperintensities supra- and infratentorially, restricted diffusion in splenium of corpus callosum | 13 |
| 55 | F | EBV-VAHS, CMV-VAHS, lymphoma | Disturbance of consciousness, meningism | NA | MRI: focal lesions in white matter | 14 |
| 57 | M | EBV-VAHS | Headache, encephalopathy, hyper-reflexia, myoclonus | L: $4\times10^6$/L, Pro: 99 mg/dL | w.n.l. | 13 |
| 62 | F | Lymphoma | Headache | P: 180 mm$H_2O$, L: $0\times10^6$/L, Pro: 27.2 mg/dL | MRI: focal lesion in brainstem lesion | 14 |
| 62 | F | EBV-VAHS, CMV-VAHS | Irritability | NA | w.n.l. | 14 |
| 62 | F | EBV-VAHS | Encephalopathy, focal seizures | L: $11\times10^6$/L, Pro: 79 mg/dL | Bilateral T2 hyperintensity in the caudate and putamen and RT2 hyperintensity in the external capsule | 13 |
| 62 | M | NA | Cranial nerve palsies | P: 180 mm$H_2O$, L: $0\times10^6$/L, Pro: 63.2 mg/dL | MRI: meningeal enhancement | 14 |
| 65 | M | CMV-VAHS, Lymphoma | Disturbance of consciousness | NA | w.n.l. | 14 |
| 69 | F | NA | Limb paralysis, cranial nerve palsies | NA | MRI: focal lesion in brainstem, without enhancement | 14 |
| 72 | F | NA | Disturbance of consciousness | P: 300 mm$H_2O$, L: $0\times10^6$/L, Pro: 57 mg/dL | w.n.l. | 14 |
| 73 | M | EBV-VAHS | Encephalopathy, unilateral tremor, dysarthria | L: $9\times10^6$/L, Pro: 73 mg/dL | MRI: Diffuse pachymeningeal enhancement | 13 |
| 75 | F | EBV-VAHS | Disturbance of consciousness | Pro: 69 mg/dL | w.n.l. | Present case |

Abbreviation, M; male, F; female, EBV; Epstein-Barr virus, VAHS; virus-associated hemophagocytic syndrome, CMV; Cytomegalovirus, HHV; human herpesvirus, NA; not available, P; cerebrospinal fluid pressure, L; cerebrospinal fluid leukocyte count, Pro; cerebrospinal fluid protein level, w.n.l.; Within Normal Limits.

13; J Neurol Sci. 2015; 357: 136-42.

14; Ann Hematol. 2017; 96: 1279-1285.

infection of T cells, the clinical course for chronic active EBV infection is not compatible in this case, because systematic inflammatory symptoms had not persisted for at least 3 months[15]. Histopathological examination of lymph nodes at onset revealed large numbers of T cell infiltrations, and histopathological analysis could not exclude EBV infection of T cells. Gene rearrangements for T cell receptors should have been tested to determine whether T cells were infected with EBV. Complete remission of EBV-DLBCL at 4 days before onset of HLH indicated that all our patient's symptoms were derived from HLH through EBV reactivation.

EBV-DLBCL accounts for approximately 10% of DLBCL cases, is frequently reported in Asians, and has a higher age of onset than that of general DLBCL[16–23]. In a study of the relationship between EBV-encoded small RNA (EBER), in situ hybridization (ISH), and serum EBV DNA in histopathological specimens at the time of early onset in EBV-DLBCL, six of eight EBER-ISH-positive cases were identified as EBV DNA from pretreatment PB (high titer, $>1.0 \times 10^5$ copies/mL)[24]. A correlation between EBV DNA in PB and EBER-ISH in tumor tissue has been reported[25]. Liang et al. reported that EBV-DNA negative conversion after chemotherapy would be useful for determining treatment response in patients confirmed to have increased EBV DNA at pretreatment, which also affected prognosis[25]. Periodic monitoring of EBV DNA quantification during treatment of EBV-related lymphoma may help in predicting not only treatment response and prognosis but also the risk of HLH with EBV reactivation. EBV-related antigen testing was not performed in the present case. The EBV nuclear antigen level, which increases significantly upon reactivation, may also support further diagnosis.

HLH is treated with corticosteroids and immunoglobulins, and there are cases of spontaneous remission[26–28]. However, death from multiple organ failure and neurological abnormalities can occur. Etoposide inhibits EBV proliferation by suppressing overactivated macrophages and T cells[29] and preventing production of EBV nuclear antigen[30–32]. Thus, the combination of immunosuppressive therapy with corticosteroids and cyclosporine was effective in controlling EBV-HLH[33]. Because HLH protocols suggest that combined use of etoposide and immunosuppressive therapies yields a good response, we used these treatment protocols for severe EBV-HLH[10,31,33]. However, very few studies have investigated EBV-HLH in elderly adults, and optimal treatment remains unclear. The present patient was relatively old (age 75 years) and was treated based on the HLH-2004 protocol, with the dose reduced to 50% because of severe liver dysfunction. Rituximab, used for the treatment of DLBCL, was also administered because of the possibility of HLH due to progression of EBV-DLBCL. Because EBV infects B cells, it may be effective in inhibiting EBV reactivation.

Although multidrug intervention eventually showed signs of terminating EBV-HLH, multiple organ failure progressed and impairment of consciousness persisted, resulting in multiple cerebral infarctions. EBV-DLBCL central nerve infiltration, EBV-HLH, EBV encephalitis, and EBV meningitis should be considered in the differential diagnosis for the several CNS symptoms in this case. EBV-DLBCL was the less likely cause because previous treatments were successful and disease progression was not observed. EBV encephalitis was excluded because MRI showed no characteristic finding[34,35] and there were no representative clinical symptoms. EBV meningitis, which is diagnosed by EBV DNA detection in CSF with LOC, could overlap, as similar test results and clinical symptoms were also identified in EBV-HLH with CNS. The distinction between EBV meningitis and EBV-HLH with CNS is unclear, although an autopsy can distinguish between EBV encephalitis/meningitis and EBV-HLH with CNS symptoms. The mechanism by which HLH induces CNS symptoms is believed to be influenced by hypercytokinemia; however, the details have not yet been clarified. Intrathecal administration of methotrexate may be effective for HLH presenting with CNS symptoms[36,37]; however, in this case, intrathecal administration could not be performed because of the patient's poor general condition. Early intrathecal methotrexate might have resulted in improvement. There are few reports of adult-onset EBV-HLH; thus, accumulating more data from such cases will help in the development of better treatment strategies.

**Conflict of Interest:** None.

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