



# Central nervous system involvement in adult-onset hemophagocytic lymphohistiocytosis secondary to lymphoma: a case presentation and literature analysis

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## Introduction

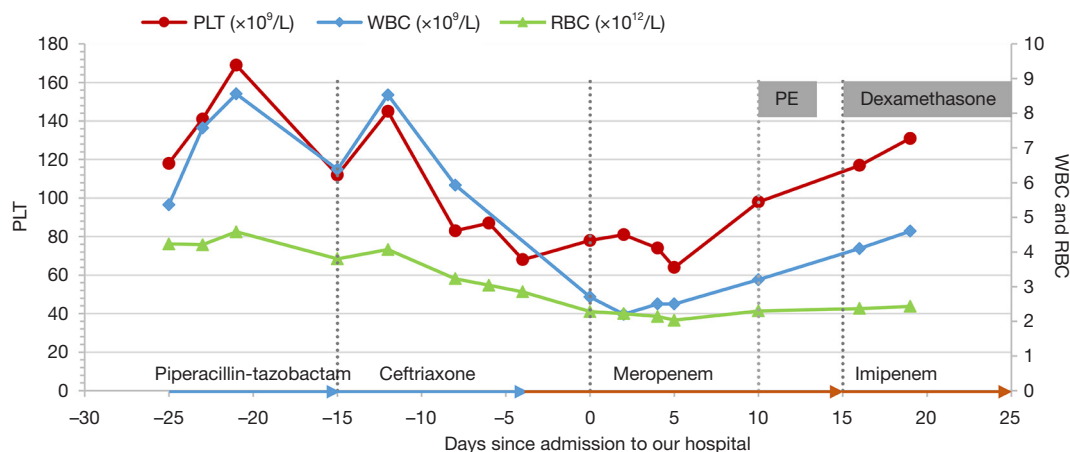
Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome characterized by activation of natural killer (NK) cells, cytotoxic T lymphocytes, and macrophages. HLH can be attributed to genetic mutations (primary HLH) or can occur secondary to an infection, malignancy, or autoimmune disorder. For adults, the most common causes are hematologic malignancies, especially T-cell/NK-cell lymphoma or leukemia (1).

Clinical and laboratory manifestations include fever, splenomegaly, cytopenia, hypertriglyceridemia, hemophagocytosis, diminished NK cell activity, hyperferritinemia, and increased sCD25 (2). In addition, central nervous system (CNS) involvement has received increasing attention. There is no precise, uniform definition of CNS-HLH, but most experts agree in suspecting CNS involvement when a patient is diagnosed with HLH with neurological symptoms or cerebrospinal fluid (CSF) abnormalities, or magnetic resonance imaging (MRI) abnormalities. MRI is an excellent tool for detecting brain lesions and is important for diagnosing and treating cranial diseases. We report a rare case of CNS involvement in adult-onset HLH secondary to diffuse large B-cell lymphoma and review the clinical and imaging features of CNS-HLH in adults.

## Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was given by the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

A 57-year-old male patient experienced repeated coughing and expectoration for 2 weeks and was diagnosed with pulmonary infection based on increased C-reactive protein level and chest computed tomography (CT) scan in October 2021 at a local hospital. Piperacillin–tazobactam was administered to control infection. Unexpectedly, the patient experienced nausea and vomiting 2 days later, followed shortly by consciousness disturbance and persistent fever (fluctuating between 38 °C and 40 °C). Thus, he was admitted to the intensive care unit of the local hospital's neurology department with suspected encephalitis. Lumbar puncture and CSF testing were performed. Autoimmune encephalitis antibodies and microbial metagenomic next-generation sequencing of CSF were negative. Brain MRI showed abnormal signals in the brain stem, left temporal lobe, and subcortical projections of the parietal lobe without enhancement. Previously, in 2013, the patient had been



**Figure 1** Timeline of dynamic changes in blood cell counts and treatment. PE, plasma exchange; PLT, platelet; WBC, white blood cell; RBC, red blood cell.

diagnosed with viral encephalitis because of headache and unresponsiveness, and the observation of left parietal and occipitotemporal gyrus lesions according to brain MRI (Figure S1).

The patient was transferred to Xiangya Hospital owing to the failure of anti-infective therapy, persistent fever, and disturbance of consciousness.

Physical examination revealed consciousness between somnolence and sopor, disorientation of time and location, impaired memory, dyscalculia, and grade 4 muscle strength in all 4 limbs. Complete blood count (CBC) showed progressive pancytopenia (Figure 1). Laboratory tests further revealed that the patient had progressive pancytopenia together with elevated levels of serum ferritin,  $Ca^{2+}$ , and interleukin (IL)-10. Following consultation with a hematologist, HLH was identified as a potential diagnosis in this case. Further tests showed elevated sCD25 levels and reduced NK cell activity. There was no serologic evidence of cytomegalovirus, hepatitis, tuberculosis, HIV, or Epstein-Barr virus (EBV) infection. B-ultrasound examination showed splenomegaly but without enlarged lymph nodes. Positron emission tomography-CT (PET-CT) did not disclose abnormal glucose metabolism of malignant solid tumors. CSF examination showed a high total protein content (0.73 g/L, reference = 0.15–0.45 g/L) and a slightly increased immunoglobulin G level (0.05 g/L, reference = 0–0.03 g/L). Owing to the progressive neurological symptoms, cranial MRI was ordered and demonstrated abnormal signals throughout the cortical and subcortical regions of the telencephalon and pontine (Figure 2), which

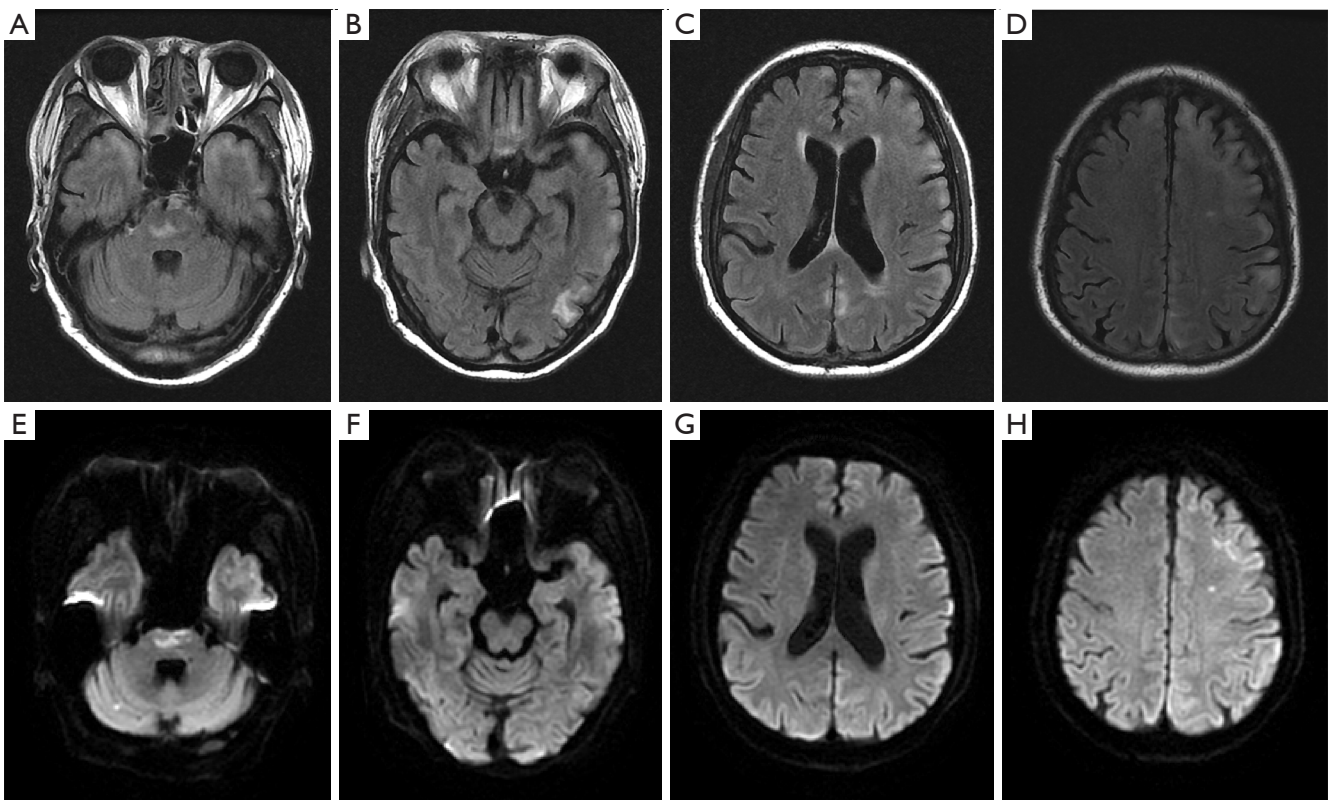
had some similarities with the MRI findings in 2013.

The patient fulfilled 6 of the 8 diagnostic criteria for HLH. In adult patients, the vast majority of HLH cases are secondary, so bone marrow aspiration biopsy was performed to determine the cause of HLH in this patient. Flow cytometry assessment of the bone marrow demonstrated 1.5% clonal B cells in nucleated cells, resulting in a pathological diagnosis of diffuse large B-cell lymphoma after immunohistochemistry (Figure 3). Dexamethasone was administered under the guidance of the hematologist in November 2022, and the patient's temperature gradually decreased.

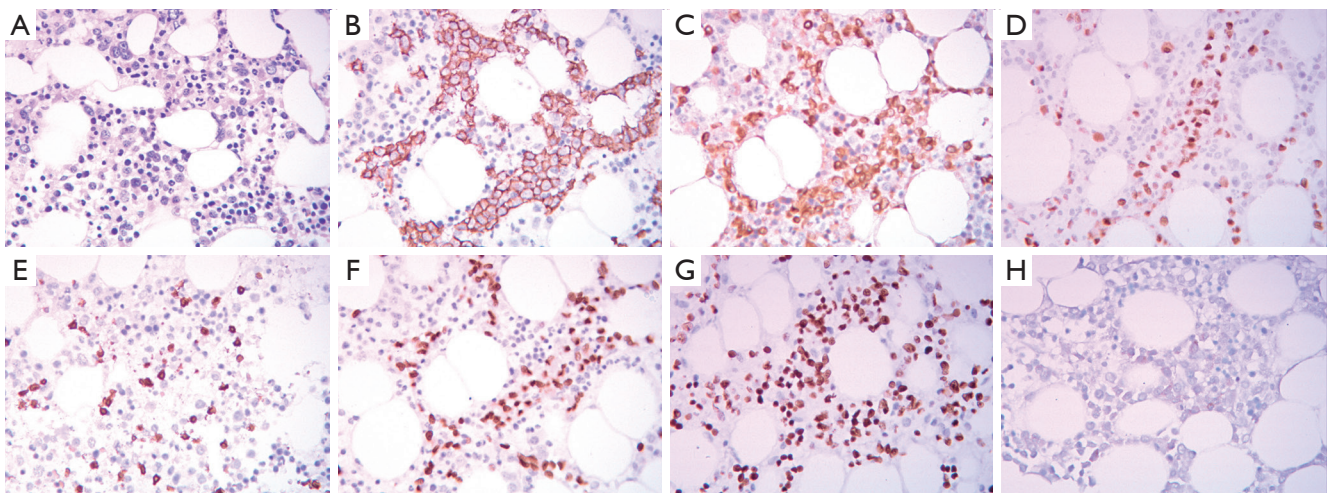
The patient was additionally treated with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) in the hematology department. MRI performed 3 months later showed significant regression of the intracranial lesions (Figure 4). Clinically, the patient had few neurologic symptoms, except for a slightly blunted response and impaired memory. As of this writing, he is still being followed up at our hospital.

## Discussion

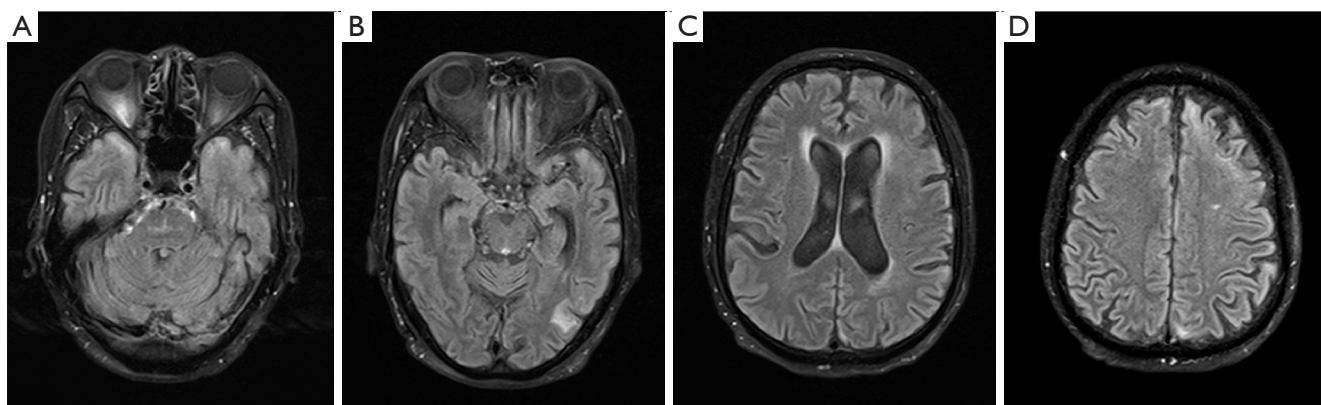
Despite treatment for suspected pulmonary infection, the patient still had a fever and disturbance of consciousness. MRI revealed multiple lesions, but there was no evidence of CNS infection or autoimmune diseases of the CNS. The progressive decline of the CBC, elevated serum ferritin and IL-10 levels, splenomegaly, and hyperpyrexia revealed the possibility of HLH. An elevated sCD25 level and reduced



**Figure 2** Magnetic resonance imaging in November 2021. (A-D) Initial axial, fluid-attenuated inversion recovery sequences demonstrated hyperintensity involving the pons, cortical, and subcortical regions. (E-H) Diffusion-weighted imaging showed high intensity in some lesions, but without low signal on apparent diffusion coefficient (not shown).



**Figure 3** Results of HE staining, immunohistochemistry, and EBER *in situ* hybridization of bone marrow. (A) HE-stained bone marrow (A, 400 $\times$ ). (B-G) Immunohistochemical staining: lymphocytes were positive for CD20 (B, 400 $\times$ ), BCL-2 (C, 400 $\times$ ), MUM1 (D, 400 $\times$ ), and Pax-5 (F, 400 $\times$ ) but negative for CD5 (E, 400 $\times$ ). The Ki-67 labeling index was >80% (G, 400 $\times$ ). (H) EBER *in-situ* hybridization showed lymphocytes were negative (400 $\times$ ). HE, hematoxylin-eosin; EBER, Epstein-Barr encoding region.



**Figure 4** (A-D) Magnetic resonance imaging in February 2022 revealed improvement and recovery according to fluid-attenuated inversion recovery.

NK cell activity further supported this diagnosis. In adults, most cases of HLH are secondary to infections, tumors, or autoimmune disorders. In this case, there was no evidence of viral infection, especially EBV, or autoimmune diseases. After hematology consultation, abnormal phenotype B cells were found in the bone marrow with flow cytometry, and further bone marrow biopsy revealed diffuse large B-cell lymphoma. Thus, the HLH was confirmed as being secondary to diffuse large B-cell lymphoma.

Among children with HLH, 47–73% present with manifestations of neurological involvement (3,4), which is a marker of poor prognosis in children (5,6). On the other hand, 10% of adults with HLH have CNS involvement (7), so this patient represents a rare case of CNS-HLH. Because of the atypical initial clinical presentation of cough, expectoration, fever, and CNS symptoms, as well as abnormal cortical and subcortical signals on MRI, alternative diagnoses were considered. These included viral meningitis, autoimmune encephalitis, mitochondrial disease, and malignancy.

We searched the literature for cases of CNS-HLH with detailed MRI data that had been independently analyzed by 2 doctors. The underlying cause in 5 of 21 cases could not be found or was not mentioned. The mean age of the 21 patients was  $43 \pm 17$  years, and there were 11 (52%) women. The most common clinical manifestations were consciousness disturbance (15/21) and seizures (11/21) (*Table 1*). In CSF examination, a mildly elevated white blood cell count with lymphocyte predominance and a mildly elevated protein content were found, although some patients exhibited normal CSF. Excluding the 2 cases of diffuse cerebral hemorrhage (*Table 1*), *Table 2* summarizes

the characteristics of the remaining 19 cases. Most lesions on MRI were multiple (*Table 2*) and mainly located in the supratentorial area, and almost none involved the infratentorial area alone. Of the 19 cases, deep white matter (14/19) was most frequently involved, followed by cortical or subcortical white matter (10/19), periventricular white matter (8/19), basal ganglia (8/19), and pons (5/19). Hemorrhage, perhaps due to perivascular infiltration causing injury, was reported in some cases (5/21) (7,9,25,26). Enhancement and diffusion restriction of the lesion was also reported in some cases. A Chinese retrospective case series showed that consciousness disturbance and focal lesions in the cortical and adjacent subcortical regions were the most common signs, but the proportion of diffusion restriction and enhancement was significantly higher than that encountered in our literature review (7). According to histological examination of the brain, CNS-HLH is characterized by CD8<sup>+</sup> T cell infiltration of the parenchymal and perivascular tissues, which activate macrophages. Most patients were treated with the guideline-directed HLH-1994 or HLH-2004 protocol, and achieved remission (12/19). Interestingly, most reported deaths were attributed to complications such as infection rather than CNS deterioration.

Secondary CNS lymphoma mostly involves deep gray or white matter, and lesions show enhancement on enhanced T1-weighted image and diffusion restriction (27,28). The patient described in this report had no limited space-occupying lesions and no enhancement, which is inconsistent with lymphoma. Despite the lack of a brain biopsy, based on the clinical presentation and imaging findings, we deemed that the lesions observed by MRI were CNS-

**Table 1** Summary of cases of adult-onset HLH involving the CNS

Author	Sex	Age, years	Neurological symptoms	Underlying condition	Brain pathology	CSF findings	MRI findings	Treatment	Prognosis
Ruppert <i>et al.</i> (8)	F	28	Obtunded, comatose	SLE	–	–	FLAIR: abnormal signals in bilateral thalami, adjacent portions of the posterior limb of the internal capsule bilaterally, midbrain, pons, medulla, and bilateral middle cerebellar peduncles	Cyclosporin A, dexamethasone, etoposide, IT-MTX, IVIG	Improved
Gratton <i>et al.</i> (9)	M	38	Disorientation, somnolence, spastic tetraparesis, seizure, cognitive slowing	Ankylosing spondylitis, SLE	–	WBC: 2 (100% L) Pro: 147 mg/dL	FLAIR: increased signal in the basal ganglia and patchy periventricular and subcortical white matter hyperintensities DWI: scattered punctate foci of restricted diffusion Contrast-enhanced T1: nodular enhancement in the basal ganglia and periventricular white matter	Cyclosporine, dexamethasone, etoposide	Improved
Gratton <i>et al.</i> (9)	F	62	Encephalopathy, seizure	Rheumatoid arthritis, EBV infection	–	WBC: 11 (77% L) Pro: 79 mg/dL	FLAIR: hyperintensity in the basal ganglia, external capsule, periventricular white matter	Dexamethasone, etoposide, rituximab	Improved, but anemia and failure to thrive
Gratton <i>et al.</i> (9)	F	21	Seizure	Malaria	–	WBC: 43 (24% L) Pro: 1,206 mg/dL	FLAIR: hyperintensity in the basal ganglia, external capsule, cortex, and subcortical white matter SWI: hemorrhage in left temporal–occipital lobe	Dexamethasone, cladribine, IVIG	Died after prolonged hospital course because of complications
Pastula <i>et al.</i> (10)	M	55	Disequilibrium, gait unsteadiness, left foot drop, right-hand paresthesia, seizure	Unknown	Brain autopsy: profound histiocytic infiltration, perivascular lymphocytosis, emperipolesis	WBC: 1 Pro: 69 mg/dL	FLAIR: hyperintensity in supra- and infratentorial areas involving the cortex and juxtacortical white matter Contrast-enhanced T1: cortical enhancement	Solumedrol, steroid, PE	Died 1 year after diagnosis because of aspiration pneumonia
Gold <i>et al.</i> (11)	M	63	Seizure, left hemiparesis, deteriorating mental status	Rheumatoid arthritis	–	WBC: 4 (52% L) Pro: 82 mg/dL	FLAIR: hyperintensity in the right frontal and parietal cortical regions and throughout the subcortex	Dexamethasone, cyclosporine, etanercept, PE	Improved
Anderson <i>et al.</i> (12)	F	56	Encephalopathy	Unknown	–	Pro: 40 mg/dL	FLAIR: hyperintensity in bihemispheric white matter and basal ganglia DWI: diffusion restriction Contrast-enhanced T1: enhancement	Steroid, chemotherapy	Died 6 years after diagnosis because of polymicrobial bacteremia
Magaki <i>et al.</i> (13)	M	41	Altered mental status, headache, apraxia, coma	EBV infection	Brain autopsy: lymphocytic inflammation, necrosis, gliosis, focal hemorrhage	WBC: L↑ Pro: >620 mg/dL	FLAIR: hyperintensity in multifocal, gyriform cortical, diffusion restriction Contrast-enhanced T1: hyperintensity in multifocal, gyriform cortical, subtle enhancement	Dexamethasone, etoposide, acyclovir, methotrexate, ganciclovir	Death from CNS relapsing
Barmettler <i>et al.</i> (14)	F	24	Unresponsive, seizure	Familial HLH	–	–	FLAIR: hyperintensity in periventricular and subcortical white matter	Antibiotics, IVIG, prednisone, anakinra, cyclosporin A, dexamethasone, etoposide	Died after 44 days in hospital because of intracranial hemorrhage with herniation
Shah <i>et al.</i> (15) <sup>‡</sup>	M	25	Confusion, seizure	Cutaneous T-cell lymphoma	Brain biopsy: encephalitis	Histiocytes and hemophagocytosis	FLAIR: diffuse white matter signal in the right temporal, occipital and parietal lobes, edema SWI: hemorrhage in left anterior capsular/caudate	Alemtuzumab, etoposide, dexamethasone, IT-MTX	Improved
Algahtani <i>et al.</i> (16)	M	20	Headache, decrease in vision, seizure	Familial HLH	–	Pleocytosis Pro: 0.76 mg/dL	FLAIR: multiple confluent white matter demyelinating lesions in both cerebral hemispheres (mostly involving the parietal and occipital lobes), corpus callosum, cerebellar hemispheres, dorsal pons, brain volume loss Contrast-enhanced T1: nodular and linear enhancement	Steroid, PE, cyclosporin A, dexamethasone, etoposide, allogeneic stem cell transplantation	–
Han <i>et al.</i> (17)	F	52	Alert, abnormal behavior, seizure	Infection	–	IgG: 43.6 mg/dL	FLAIR: hyperintensity in bilateral deep white matter	Doxorubicin, etoposide, methylprednisolone	>6 months no seizures or limb convulsions
Verma <i>et al.</i> (18) <sup>‡</sup>	F	68	Confused, forgetful, seizure	Intravascular large B-cell lymphoma	–	Macrophages: ↑	FLAIR: hyperintensity in the right hemisphere, medial left occipital lobe, and pons	Dexamethasone, etoposide, IT-MTX, hydrocortisone, rituximab, cyclophosphamide, doxorubicin, prednisone	Improved

Table 1 (continued)

Table 1 (continued)

Author	Sex	Age, years	Neurological symptoms	Underlying condition	Brain pathology	CSF findings	MRI findings	Treatment	Prognosis
Radmanesh <i>et al.</i> (19) <sup>†</sup>	F	44	Altered consciousness	Unknown	–	–	SWI: innumerable microscopic and small hemorrhages	Dexamethasone, etoposide	Improved
Oppegard <i>et al.</i> (20) <sup>‡</sup>	F	70	Encephalopathy, visual hallucinations, diplopia, gaze	Intravascular large B-cell lymphoma	–	WBC: 5 Pro: 89 mg/dL	T2: hyperintensity in the pons and supratentorial lesions	Antimicrobials, etoposide, IT-MTX, R-CHOP	–
Hirald <i>et al.</i> (21)	M	43	Disturbance of consciousness, cognitive and language impairment, left limbs hemiparesis, seizure	Unknown	Brain biopsy: lymphohistiocytic parenchymal and perivascular inflammatory infiltrates and foci of necrosis with macrophages	WBC: 2 (100% L) Pro: 90 mg/dL	T2: heterogeneous mass located in the right hemisphere parenchyma with associated vasogenic edema  Contrast-enhanced T1: leptomeningeal enhancement and nodular enhancement in right basal ganglia and subcortical white matter	Antibiotherapy, acyclovir, corticosteroids, anakinra	Improved
Fohle <i>et al.</i> (22)	M	51	Lightheadedness, confusion	Unknown	Brain biopsy: no evidence of malignancy or infection	–	FLAIR: hyperintensity in the right frontal lobe with a small hemorrhagic focus	Dexamethasone, etoposide, prophylactic Bactrim DS, acyclovir	Recovered
Lehrer <i>et al.</i> (23) <sup>‡</sup>	F	32	Headache, irritability, right leg weakness, urinary hesitancy	Anaplastic large cell lymphoma	–	WBC: 11 (48% L) Pro: 56.4 mg/dL	FLAIR: hyperintensity in the basal ganglia, lateral ventricles, and corona radiata  Contrast-enhanced T1: enhancement in the gangliocapsular region, temporal lobe, and corona radiata	IT-MTX, anakinra, dexamethasone, CHOP-E	Sustained remission
Southam <i>et al.</i> (24)	F	22	Diplopia, hemianesthesia, hemiparesis, incoordination, headache, tremor	Familial HLH	–	WBC: ↑ Pro: ↑	T2: hyperintensity in the cerebellar hemispheres and white matter with leptomeningeal involvement	Dexamethasone, etoposide, IT-MTX	Died 2.5 years after diagnosis because of infectious complications
Southam <i>et al.</i> (24) <sup>†</sup>	M	30	Dysarthria, hemiplegia, cognitive decline	Familial HLH	–	–	SWI: hemorrhage involving unilateral thalamus and midbrain and innumerable microhemorrhages	Cyclosporin A, dexamethasone, etoposide, IT-MTX, rituximab	Died several years after diagnosis
Present case <sup>‡</sup>	M	57	Disturbance of consciousness, anomalous behavior	Diffuse large B-cell lymphoma	–	Pro: 73 mg/dL	FLAIR: hyperintensity in the pons and cortical and subcortical of the telencephalon, cerebral atrophy Contrast-enhanced T1: no enhancement  DWI: no diffusion restriction	Dexamethasone, PE, R-CHOP	Improved

<sup>†</sup>, MRI indicated diffuse cerebral hemorrhage; <sup>‡</sup>, CNS involvement in HLH secondary to lymphoma. HLH, hemophagocytic lymphohistiocytosis; CNS, central nervous system; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus; EBV, Epstein–Barr virus; WBC, white blood cell; L, lymphocytes; Pro, protein; FLAIR, fluid-attenuated inversion recovery; DWI, diffusion-weighted imaging; SWI, susceptibility-weighted imaging; IT-MTX, intrathecal methotrexate; IVIG, intravenous immunoglobulin; PE, plasma exchange; R-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab; CHOP-E, cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide.

**Table 2** MRI findings in adult-onset HLH involving CNS<sup>†</sup>

MRI findings	No. of cases
Lesion localization	
Supratentorial	12/19
Infratentorial	0/19
Both	7/19
Quantity of lesions	
Solitary	0/19
Multiple	17/19
Diffuse infiltrative	2/19
Lesion enhancement <sup>‡</sup>	7/19
Diffusion restriction <sup>§</sup>	2/19
Lesion localization details	
Periventricular white matter	8/19
Deep white matter	14/19
Cortical and/or subcortical regions	10/19
Thalamus	1/19
Basal ganglia	8/19
Pons	5/19
Cerebellar	3/19
Meningeal	2/19
Hemorrhage	5/19

<sup>†</sup>, statistics based on MRI provided in the article. <sup>‡</sup>, presence of enhancement was assessed in only 9 patients, and there was no enhancement in 2 patients. Enhancement-weighted imaging was not mentioned for the others. <sup>§</sup>, presence of diffusion restriction was assessed in only 2 patients; diffusion restriction was reported in 3 patients but without diffusion-weighted imaging in the study. Diffusion-weighted imaging was not mentioned in the others. HLH, hemophagocytic lymphohistiocytosis; CNS, central nervous system; MRI, magnetic resonance imaging.

HLH rather than lymphoma. Few studies have reported CNS involvement in HLH secondary to lymphoma. We searched the literature for studies on CNS involvement in HLH secondary to lymphoma that provided detailed MRI data (15,18,20,23) (*Table 1*). The mean age of the 5 patients (including the present patient) was 50±21 years, and 3 were female (60%). Neurological symptoms and CSF changes were similar to other cases of secondary HLH, and CSF flow cytometry showed lymphoma infiltration in 1 case. Imaging showed that white matter lesions (5/5) and pons

(3/5) were more common, with punctate enhancement reported in 1 case and diffusion restriction in 1 case. Notably, HLH secondary to intravascular large B-cell lymphoma (IVLBCL) was the most common. It has been reported that neurological symptoms are present in 35% of patients with IVLBCL, lesions mostly involve the pons, and the number of patients with a hyperintense lesion in the pons with HLH is higher than that without HLH (29). The clinical features of IVLBCL include a hemophagocytic syndrome-associated variant (30). Therefore, it is difficult to definitively determine whether CNS symptoms are caused by HLH or IVLBCL, but it is clear that HLH can aggravate intracranial lesions. The underlying disease increases the complexity of the MRI findings. Thus, the CNS symptoms and MRI findings should be considered in conjunction with other tests in the early stage, and a brain biopsy should be considered if diagnosis is difficult.

This patient had neurological symptoms in 2013, and MRI showed similar cortical and subcortical involvement to the episode described here. Thus, we should consider the possibility that the “encephalitis” developed 8 years ago was associated with HLH, but this is hard to confirm. Similar observations have been reported in the literature: a patient with CNS-HLH of unknown cause had a similar MRI lesion 10 years earlier, which was also deemed to be an acute-on-chronic manifestation of CNS-HLH (10). Therefore, we believe that MRI can provide more information than expected, and the diagnosis of HLH can be considered in the absence of systemic features.

## Conclusions

If prominent fever and neurological symptoms occur in combination with the observation of multiple lesions involving the cortex and subcortex, periventricular white matter, and basal ganglia on MRI, then encephalitis, autoimmunity encephalitis, infection, and diagnosis of HLH syndrome should be considered. We report a rare case of hemophagocytic syndrome secondary to B-cell lymphoma involving the CNS and have summarized the features of MRI in adult-onset HLH. The most common clinical manifestations of CNS-HLH in adults are impaired consciousness and seizures. Most of the brain lesions are located in the white matter and basal ganglia. Importantly, the underlying disease increases the complexity of MRI findings. We believe future larger-sample studies with an analysis of MRI features grouped according to the underlying disease would yield insightful findings.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://qims.amegroups.com/article/view/10.21037/qims-22-1151/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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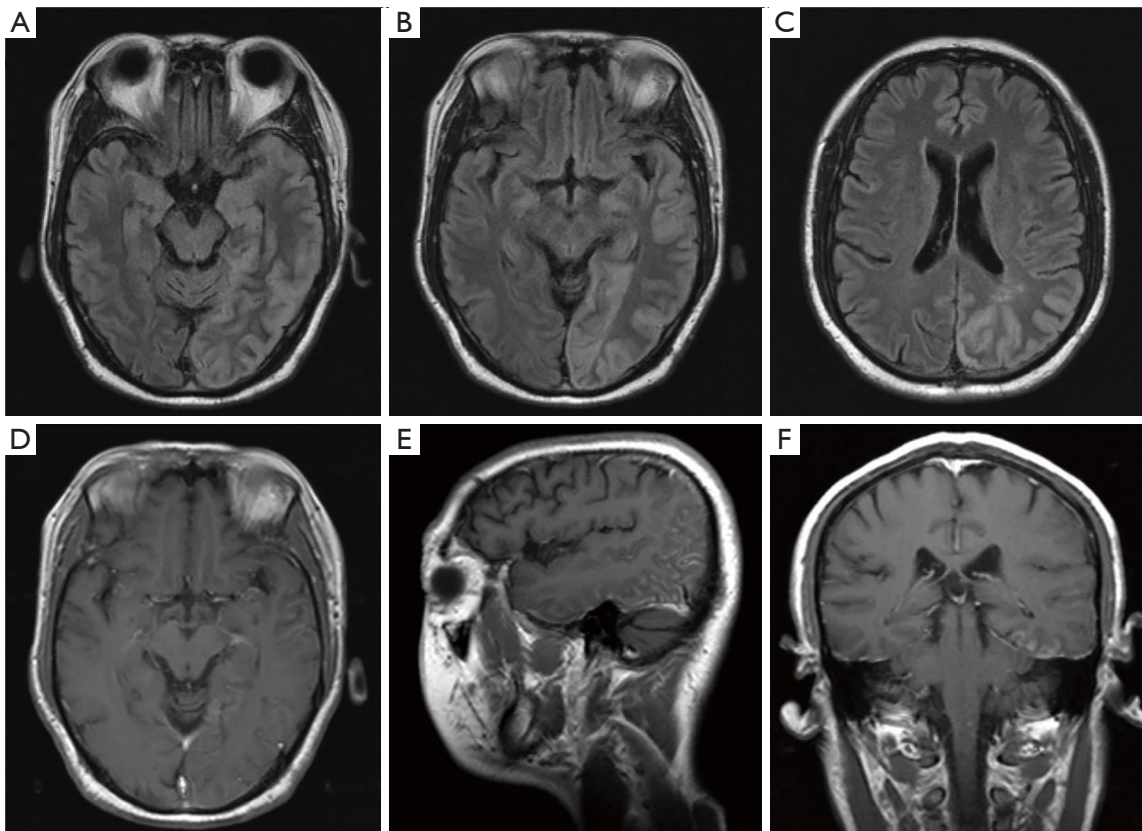
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**Figure S1** Magnetic resonance imaging in 2013. (A-C) Fluid-attenuated inversion recovery showed hyperintensity in the left parietal and occipitotemporal gyrus lesions. (D-F) Enhanced T1-weighted imaging showed the enhancement of lesions.