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【 CASE REPORT 】

The Complete Remission of Acquired Immunodeficiency Syndrome-associated Isolated Central Nervous System Lymphomatoid Granulomatosis: A Case Report and Review of the Literature

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Abstract:

A 49-year-old man presented with gradually progressive aphasia one month after being diagnosed with acquired immunodeficiency syndrome (AIDS). Brain magnetic resonance imaging showed multiple brain lesions with punctate and linear enhancement. A polymerase chain reaction detected Epstein-Barr virus (EBV) in the patient's cerebrospinal fluid. A diagnosis of isolated central nervous system lymphomatoid granulomatosis (CNS-LYG) was made based on the brain biopsy findings. The complete remission of CNS-LYG was achieved by anti-retroviral therapy (ART) alone. In the present case, the development of AIDS-associated CNS-LYG was considered to have been initiated by the reactivation of EBV in the CNS under immunosuppressive conditions. The patient's condition improved with the reconstitution of the patient's immune system.

Key words: lymphomatoid granulomatosis, central nervous system, acquired immunodeficiency syndrome, anti-retroviral therapy, Epstein-Barr virus

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Introduction

Lymphomatoid granulomatosis (LYG) is a rare lymphoproliferative disease, which is histopathologically characterized by angiocentric, angioinvasive and extranodal lesions with polymorphic lymphocyte infiltration (1). LYG is usually considered to be a systemic disease (Systemic-LYG) that predominantly involves the lungs followed by the kidneys, liver, skin and brain. However, a small number of patients with isolated LYG of the central nervous system (CNS-LYG) have been reported (2-13). In contrast to systemic-LYG, which is recognized as an Epstein-Barr virus (EBV)-related B cell lymphoproliferative disease (14), CNS-LYG is considered to be a heterogeneous disorder and is not associated with EBV infection in most cases (8, 15). We herein report a case of acquired immunodeficiency syndrome (AIDS)-associated CNS-LYG. A polymerase chain reaction (PCR) revealed that the patient's cerebrospinal fluid (CSF) was positive for EBV. Although CNS-LYG has been reported to be associated with a poor prognosis in AIDS patients (2-7), in the present case, a complete remission was achieved with anti-retroviral therapy (ART).

Case Report

A right-handed 49-year-old Japanese man who was affected by *Pneumocystis* pneumonia was diagnosed with AIDS. At one month after the remission of pneumonia, he noticed speaking difficulty. ART [dolutegravir (50 mg), abacavir (600 mg), and lamivudine (300 mg)] for AIDS was initiated 20 days after the onset of neurological symptoms.

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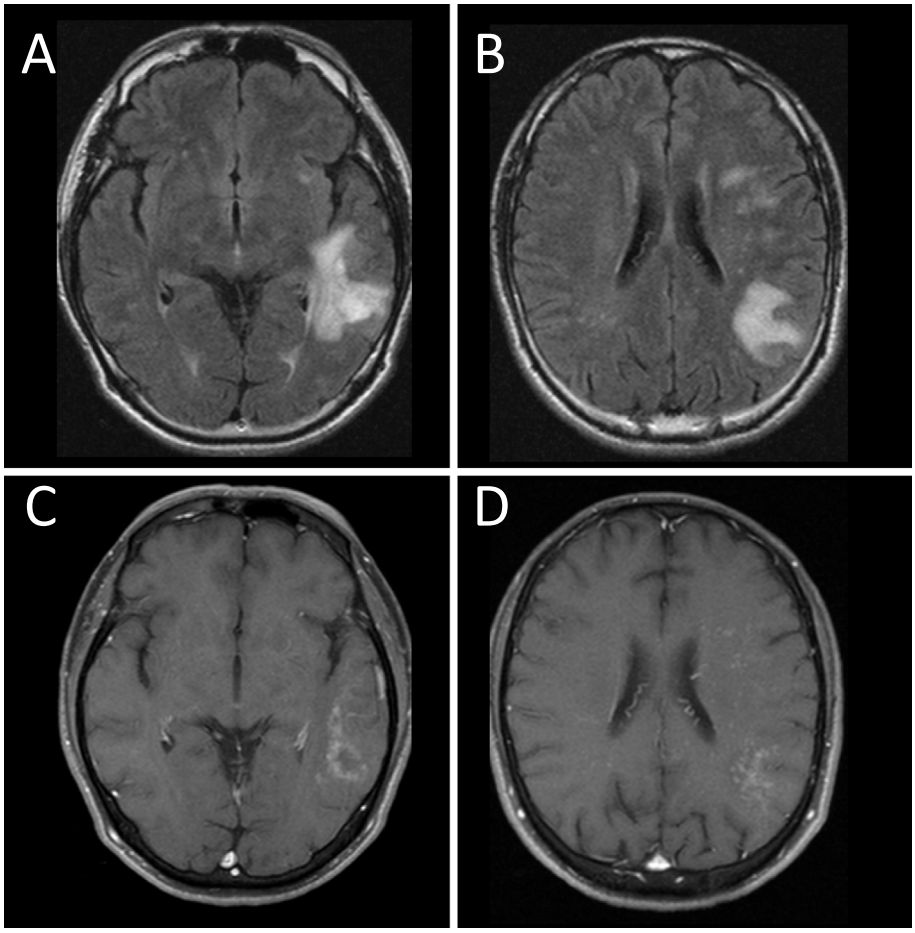

Figure 1. Brain MRI findings at admission. Fluid-attenuated inversion recovery (FLAIR) imaging showed multiple high-intensity lesions in the left parietal and temporal lobes (A, B). Gadolinium-enhanced T1-weighted imaging revealed multiple punctate and linear enhancement (C, D).

Brain magnetic resonance imaging (MRI) showed multiple brain lesions predominantly in the left parietal and temporal lobes. His condition gradually deteriorated and the brain lesions expanded. At 2 months after the onset of neurological symptoms, he was admitted to our hospital.

A physical examination revealed that his vital signs were normal, and neither lymphadenopathy nor hepatosplenomegaly was observed. A neurological examination revealed mild sensory aphasia and incomplete Gerstmann syndrome (dyscalculia, finger agnosia, and left-right disorientation). The laboratory findings were as follows: white blood cell count, 4,380/μL; hemoglobin, 14.0 g/dL; platelets, 22.3×10^{4}/μL; lactate dehydrogenase, 143 U/L; CD4-positive cell count, 240/μL; human immunodeficiency virus (HIV) ribonucleic acid, 62 copies/mL. The levels of angiotensin converting enzyme, anti-neutrophil cytoplasmic antibody, and soluble interleukin-2 receptor were within the respective normal ranges. The detection of EBV antibodies indicated a prior infection. A PCR revealed that the patient's peripheral blood was negative for EBV. A CSF analysis showed a normal cell count (2/μL), an increased protein level (94 g/dL) and a normal glucose level (65 mg/dL). Culturing and a cytological analysis of the CSF yielded no remarkable results. A PCR of the CSF was positive for EBV and negative for JC virus. Chest and abdominal computed tomography revealed no abnormal findings (including abnormal lung lesions). Brain MRI showed multiple high-intensity lesions that were mainly located in the left parietal and temporal lobes on T2-weighted and fluid-attenuated inversion recovery imaging (Fig. 1A, B) with multiple punctate and linear enhancement (Fig. 1C, D). The brain lesions were found to have increased in size in comparison to the previous MRI examination (Fig. 2).

One month after admission, open brain biopsy was performed from the left temporal lobe to further investigate the patient's condition. The biopsied tissue showed the angiocentric infiltration of small lymphocytes, which was associated with the infiltration of the surrounding brain parenchyma by large numbers of macrophages and some plasma cells (Fig. 3A, B). The lymphocytes showed no overt nuclear atypia. An immunohistological analysis indicated that the majority of these lymphocytes were CD3-positive T cells (Fig. 3C). An increased number of CD8-positive T cells was also noticed (Fig. 3E, F), while the number of CD20-positive B cells was small (Fig. 3D). Immunostaining for JC virus and EBV-encoded small ribonucleic acid *in situ* hybridization (EBER ISH) were negative. No remarkable demyelination, fibrinoid necrosis of vessels, or intranuclear in-

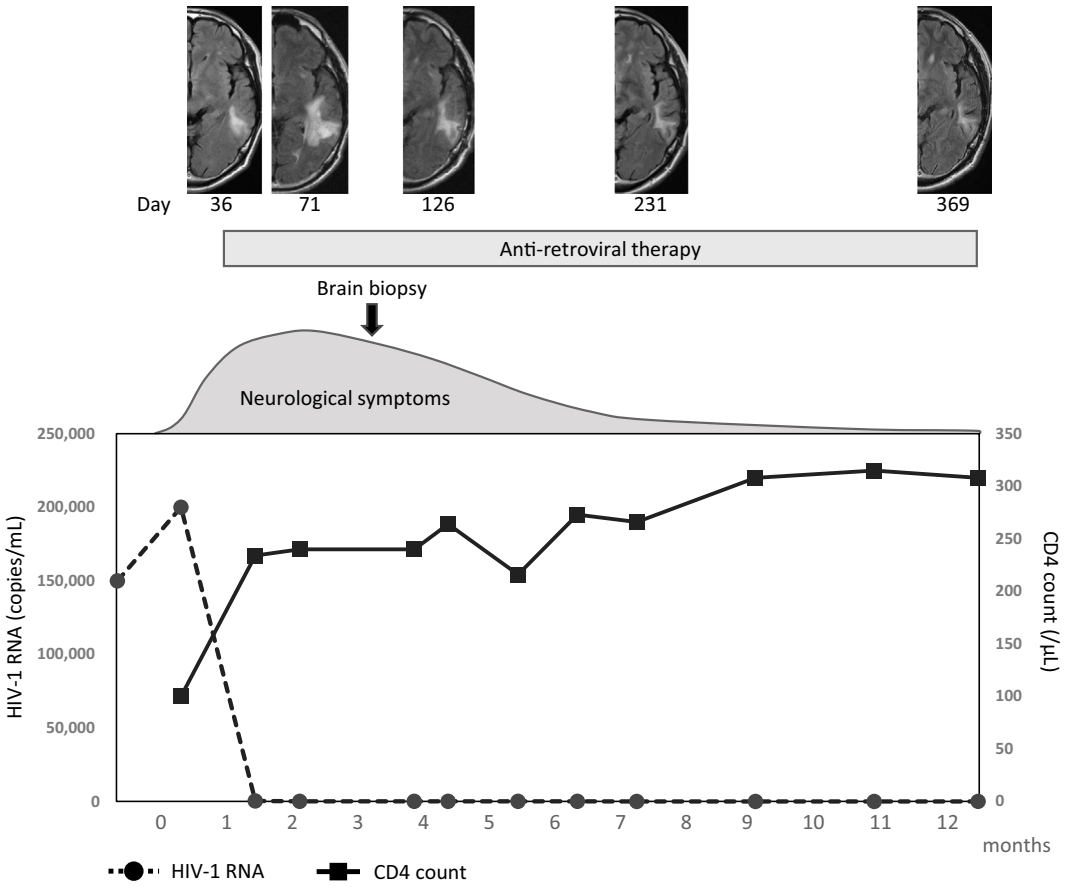

Figure 2. **The clinical course of the patient. The neurological symptoms and brain lesions on fluid-attenuated inversion recovery (FLAIR) imaging improved as the patient's CD4 count recovered and the HIV-RNA load decreased. CD: cluster of differentiation, HIV: human immunodeficiency virus**

clusions in the glial cells were observed. Furthermore, we did not detect multinucleated giant cells around the blood vessels (a characteristic of AIDS encephalopathy). Rearrangement analyses of the *T cell receptor* γ gene and *immunoglobulin heavy chain* gene indicated no evidence of monoclonality in either the T or B cells. A diagnosis of CNS-LYG was made based on the characteristic histopathological findings. Vasculitis, a common angio-destructive disease, was ruled out as neither fibrinoid necrosis nor leukocyte clasts were observed. The radiological findings were compatible with a diagnosis of CNS-LYG.

We continued ART without adding immunosuppressive therapy. Thereafter, the patient's neurological symptoms and brain MRI findings gradually improved. These changes occurred along with the reconstitution of the patient's immune system (Fig. 2). His neurological symptoms were found to have completely disappeared at 11 months after onset of CNS-LYG and no relapse was observed at up to 18 months after the onset of CNS-LYG. At 13 months after onset of CNS-LYG, a PCR revealed that the patient's CSF had become negative for EBV.

Discussion

To date, there have been six reported cases of AIDS-associated CNS-LYG (Table) (2-7). CNS-LYG appears to have a better prognosis than systemic-LYG with CNS involvement (8); however, AIDS-associated CNS-LYG appeared to be lethal, with the clinical and radiological findings deteriorating in most patients, despite treatment for AIDS and/or LYG (Table) (2-7). Interestingly, all CNS-LYG patients with AIDS showed T cell-dominant angiocentric infiltration in pathological examinations of brain tissue (Table) (3-7), similar to our patient. In addition, with the exception of two cases in which the details of EBV infection were not described (2, 3), all of the CNS-LYG patients with AIDS-including our patient-showed evidence of EBV infection with CNS involvement (4-7) (Table). Based on the clinical and pathological findings in the present and previously reported cases, AIDS-associated CNS-LYG is considered to be initiated by the reactivation of EBV in the CNS under immunosuppressive conditions, followed by the infiltration of reactive polyclonal T cells. In our patient, although EBER ISH of a brain tissue specimen was negative, a PCR detected EBV in the patient's CFS, and confirmed the reactivation of EBV in the CNS. The most likely reason for the discrepancy between the EBV PCR and EBER ISH results was the timing of examinations; the CSF PCR was performed at the fastigium of CNS-LYG, whereas the brain biopsy was performed one month later after the patient's

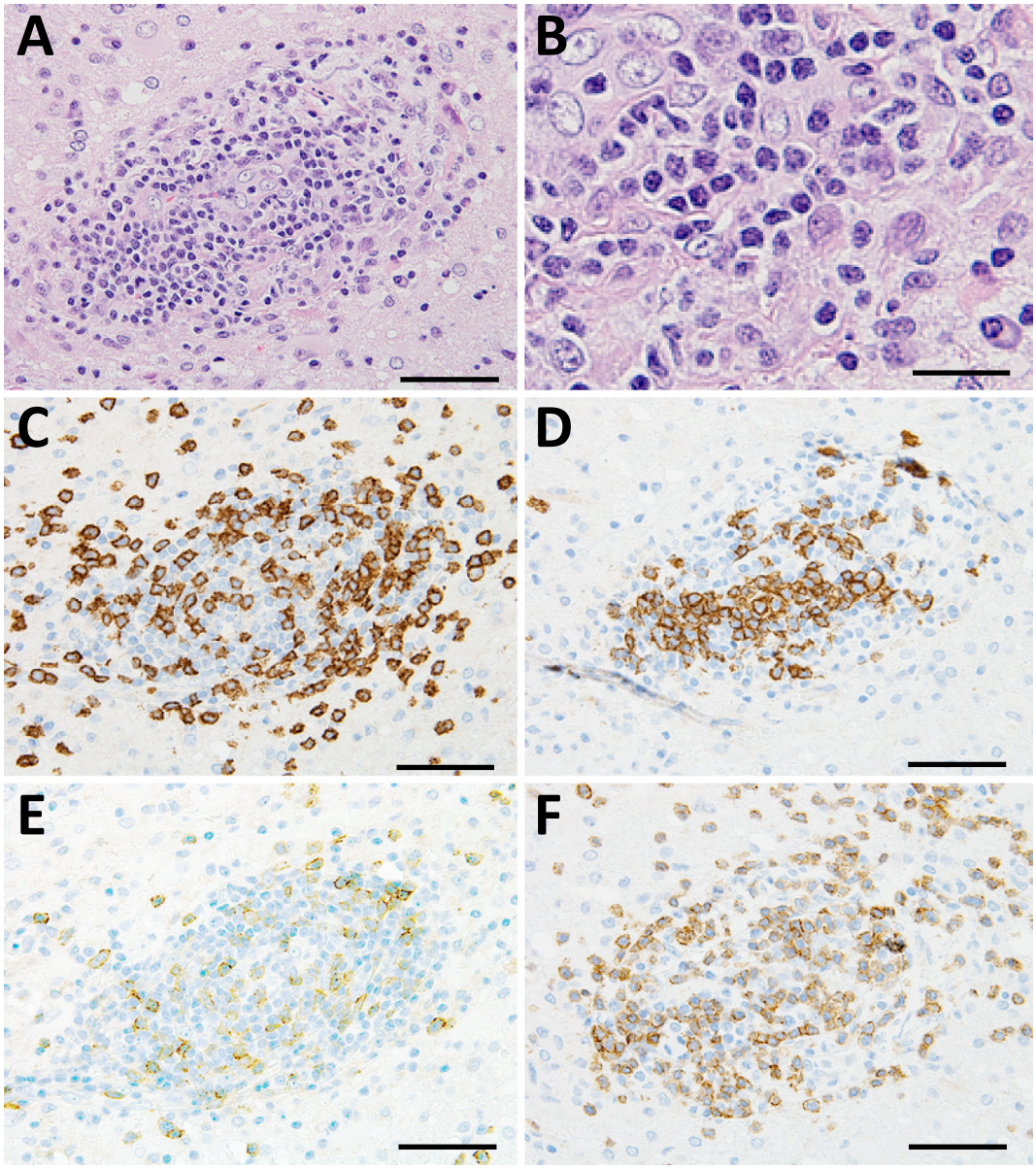

Figure 3. **The pathological findings of the biopsied brain tissue. Hematoxylin and Eosin (H&E) staining (A: low-power field; B: high-power field) and Immunohistochemical staining with anti-CD3 (C), CD20 (D), CD4 (E), and CD8 (F) antibodies. H&E staining revealed angiocentric lesions of small lymphocytes without overt nuclear atypia. The infiltration of large numbers of macrophages with some plasma cells was also observed in the surrounding brain parenchyma (A, B). Immunohistochemical staining showed the intensive infiltration of CD3-positive T cells in and around the angiocentric lesions (C), while small numbers of CD20-positive B cells were found in the perivascular lesions (D). The majority of T cells were CD8-positive (F). Scale bars: A and C-F: 50 μm, B: 20 μm**

clinical and radiological findings had started to improve (Fig. 2).

In contrast to previously reported cases of CNS-LYG, which showed a poor prognosis (2-7), in our case, a complete remission was achieved with ART. We hypothesize that ART induced moderate immune reconstitution, which suppressed EBV reactivation in the CNS but did not induce an excessive immune reaction, i.e., immune reconstitution inflammatory syndrome (IRIS)-resulting in a complete remission. In addition, the viral load of EBV is thought to influence the prognosis of AIDS-associated CNS-LYG. In our patient, EBV was detected in the patient's CSF by a PCR that was performed two months after the onset of neurological symptoms. However, EBER ISH of the biopsied brain tissue at three months after onset was negative for EBV, suggesting a low viral load. This might explain the favourable outcome in our patient.

The observations in our patient suggest that the administration of ART, the first-line therapy for HIV infection, could bring about a favourable outcome in AIDS patients with CNS-LYG. Although immunosuppressive drugs have a risk of offsetting the effect of ART and causing life-

Table. Clinical Characteristics of CNS-LYG Patients Associated with AIDS.

Reference	Age Sex	Predominant lymphocyte at the brain lesion	Clonality of lymphocyte	EBER ISH	CSF EBV PCR	IRIS	Therapy for HIV	Therapy for LYG	Clinical course
2	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
3	45 M	T cell	n.d.	n.d.	n.d.	-	-	steroid	Died three weeks after admission
4	56 M	T cell	n.d.	+	n.d.	-	ART	radiation	CNS lesions progressed despite the treatment
5	37 M	T cell	n.d.	+	n.d.	+	ART	-	Died six months after the onset of symptoms
6	44 M	T cell	n.d.	+	n.d.	+	ART	steroid	Died nine months after the onset of symptoms
7	34 M	T cell	+ (B cell)	+	n.d.	-	n.d.	n.d.	Lost to follow-up
Present case	49 M	T cell	-	-	+	-	ART	-	Complete remission at 11 months No relapse up to 18 months

CNS-LYG: isolated lymphomatoid granulomatosis of the central nervous system, AIDS: acquired immunodeficiency syndrome, EBER ISH: Epstein-Barr virus encoded small RNA *in situ* hybridization, CSF EBV PCR: polymerase chain reaction of the cerebrospinal fluid for Epstein-Barr virus, IRIS: immune reconstitution inflammatory syndrome, HIV: human immunodeficiency virus, n.d.: not described, ART: anti-retroviral therapy

threatening infection in patients with AIDS, the additional administration of steroids and immunosuppressive agents should be considered in CNS-LYG patients with IRIS (5, 6).

In conclusion, we reported the first case in which a complete remission was achieved in a patient with AIDS-associated CNS-LYG. The results suggest that ART could be a first-line therapy for AIDS-associated CNS-LYG.

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

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