

Case Study

Development of Primary Central Nervous System Lymphoma Associated with Human Immunodeficiency Virus and JC Virus Infection

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We report here a case of a 37-year-old man with human immunodeficiency virus (HIV) infection followed by JC virus (JCV) infection and primary central nervous system lymphoma (PCNSL). The patient had been infected with HIV type 1 due to blood products for hemophilia A during infancy. He had progression of nervous symptoms and was diagnosed with progressive multifocal leukoencephalopathy (PML) clinically at the age of 36, when his CD4-positive lymphocyte counts ranged between 350 and 450/ μ l. Oral mefloquine, intravenous methylprednisolone pulse therapy, and intravenous immunoglobulin were not effective for the PML, and the patient entered a vegetative state. Brain biopsy revealed JCV infection without pathological findings of PML. Eight months after the clinical diagnosis of PML, he developed respiratory failure and brain magnetic resonance imaging revealed a mass lesion in the brain stem. The patient died 19 months after the diagnosis of PML. Autopsy findings were compatible with PCNSL. EBV-encoded small RNA-1-positive cells were not detected. We present a case of JCV-positive PCNSL with HIV infection complicated with clinical PML. [*J Clin Exp Hematop* 54(3) : 211-217, 2014]

Keywords: primary central nervous system lymphoma, progressive multifocal leukoencephalopathy, acquired immunodeficiency syndrome, HIV infection

INTRODUCTION

JC virus (JCV), the causative agent of the fatal human demyelinating disease progressive multifocal leukoencephalopathy (PML), is an opportunistic papovavirus that infects and destroys oligodendrocytes.¹ Although JCV has been considered a neurotropic virus, many studies have demonstrated that it can infect lymphocytes as well.¹ JCV may be reactivated among immunocompromised individuals after human immunodeficiency virus (HIV) infection, lymphoproliferative disease, or the use of biological drugs, such as rituximab and

natalizumab.² Reactivation results in the lytic infection of oligodendrocytes in the brain and the development of PML. However, whether JCV can contribute to the onset of lymphoproliferative disease is not known.

Besides opportunistic infection, primary central nervous system (CNS) lymphoma (PCNSL) may develop in immunosuppressed patients at an increased frequency.³ Although JCV infection and PCNSL are relatively common complications of acquired immunodeficiency syndrome, cases with histological confirmation of concomitant or sequential development of these complications are extremely rare. Here, we describe a patient with hemophilia A who developed JCV infection and PCNSL consecutively during the course of HIV infection.

CASE REPORT

A 37-year-old man was admitted to our hospital because of fatigue and anorexia that had persisted for more than six months. His previous medical history included hemophilia A and HIV-1 infection through blood product transfusions in infancy. Anti-retroviral therapy (ART) was started in 1993,

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but his HIV-1 viral load (VL) had been high because of poor adherence to the prescription and leukocytopenia had been remarkable, with the number of CD4-positive lymphocytes ranging between 200 and 400 × 10⁶/L. The results of repeated tests for drug resistance to HIV-1 were negative. All kinds of effort were made to improve the patient's adherence up to 2006, when he eventually showed substantial reduction in VL in October 2006: HIV-1 RNA < 40 copies/mL. While the VL remained low, the number of CD4-positive lymphocytes ranged between 300 and 450 × 10⁶/L until December 2012 (Fig. 1).

On admission, the results of general physical examination were unremarkable. His right ankle was contracted due to hemophilic arthritis. Neurologically, he was alert and fully oriented. He had an expressionless face and spoke monotonously with a soft voice. Bradykinesia was evident. There was generalized hyperreflexia and positive snout reflexes. Babinski signs were absent. He could walk with small steps while holding onto a stand. Visual field and sensory examination results were normal. He was not incontinent in terms of urine or stool. Blood testing showed a decreased CD4-positive lymphocyte count of 257 × 10⁶/L and undetectable HIV-1 viral load. On magnetic resonance imaging (MRI), high-signal-intensity areas in a T2-weighted image (T2WI) were observed in the cerebellum, mesencephalon, basal nucleus, thalamus, corpus callosum, medulla oblongata, and cervical cord, without gadolinium-containing contrast enhancement (Fig. 2). Cerebrospinal fluid (CSF) examination showed slight elevation of protein (63 mg/dL) with a normal

cell count. JCV-DNA, cytomegalovirus-DNA, Epstein-Barr virus (EBV)-DNA, and HIV-1 RNA were not detected in the CSF by polymerase chain reaction methods. The cytology showed no malignancy and soluble interleukin-2 receptor level was 130 U/mL. The patient was clinically diagnosed with PML.

Mefloquine treatment (275 mg/day p.o. for 3 days and then 275 mg/week p.o.) was started, but his slurred speech and reduced motivation/lethargy deteriorated. The patient received methyl prednisolone (mPSL) pulse therapy (1,000 mg/day i.v. for 3 days) four times in March and April, 2012. However, the response was minimal. Intravenous administration of immunoglobulin and mPSL pulse therapy in June 2012 also did not improve the MRI findings.

In June 2012, brain biopsy was performed from the right temporal lobe lesion. This biopsy revealed mildly increased neuroglia cells without lymphocyte infiltration or degenerated lesions (Fig. 3a). On immunohistochemistry for JCV, Agno C was mainly positive in neuronal cell bodies; VP1BC was positive in nuclei, and bodies of neuronal cells and neuroglia cells; and VP2 was positive in nuclei, bodies of neuronal cells, and bodies of neuroglia cells (Fig. 3b, 3c, 3d), demonstrating the existence of JCV in the brain. However, pathological findings of PML, such as bizarre giant astrocytes and oligodendroglial intranuclear inclusions, were not observed in the biopsied tissue. Toward September 2012, the patient entered a state of akinetic mutism, and the brain lesions also showed relevant deterioration in the bilateral white matter and the left frontal cortex on MRI (Fig. 4). In November 2012,

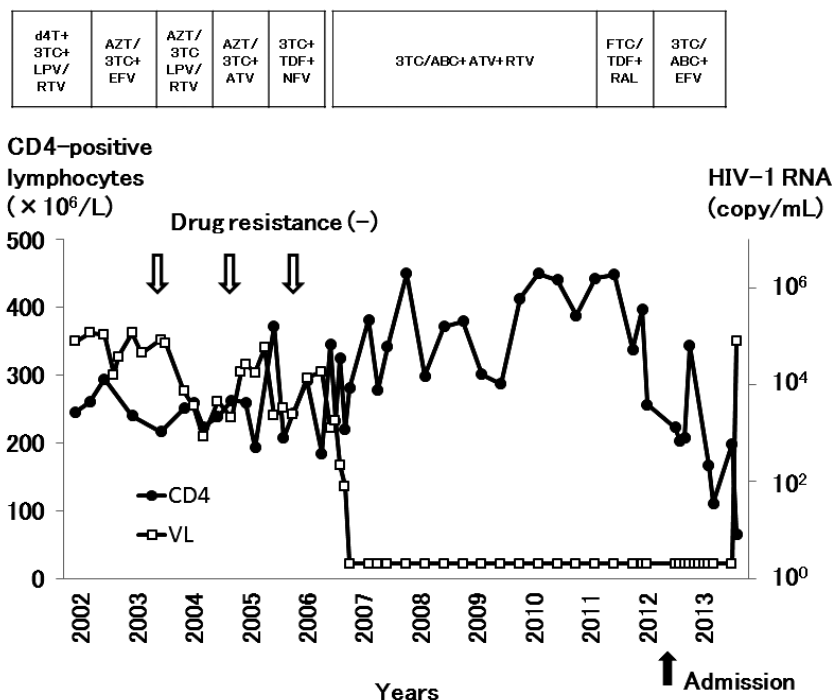


Fig. 1. The progress of the number of CD4-positive T lymphocytes and HIV-VL. From 2006 to 2012 when the diagnosis of PML was made, the number of CD4-positive T lymphocytes was greater than 250 × 10⁶/L. d4T, Stavudine; 3TC, Lamivudine; LPV, Lopinavir; RTV, Ritonavir; AZT, Zidovudine; EFV, Efavirenz; ATV, Atazanavir; TDF, Tenofovir; NFV, Nelfinavir; ABC, Abacavir; FTC, Emtricitabine; RAL, Raltegravir; HIV, human immunodeficiency virus; VL, viral load

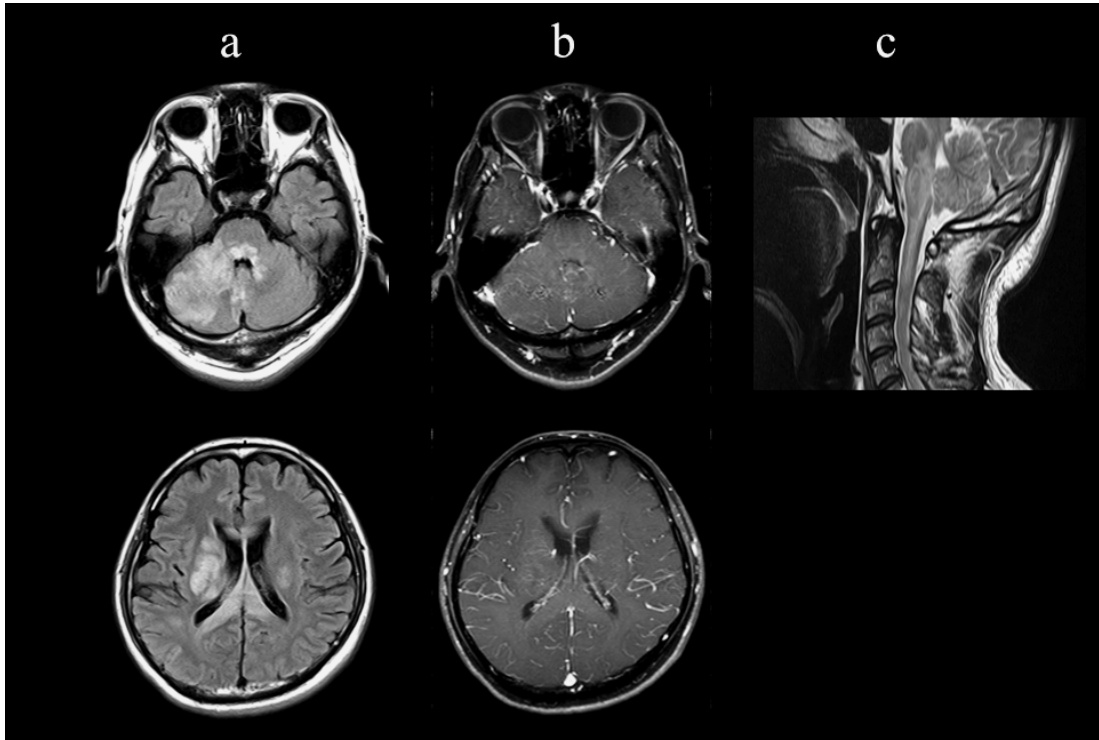


Fig. 2. Magnetic resonance imaging (MRI) in February 2012. (2a) MRI in fluid-attenuated inversion recovery (FLAIR) showed high-signal-intensity areas in the cerebellum, mesencephalon, basal nucleus, thalamus, and corpus callosum. (2b) Contrast enhancement was not observed using gadolinium. (2c) The lesion was also seen in medulla and upper cervical cord.

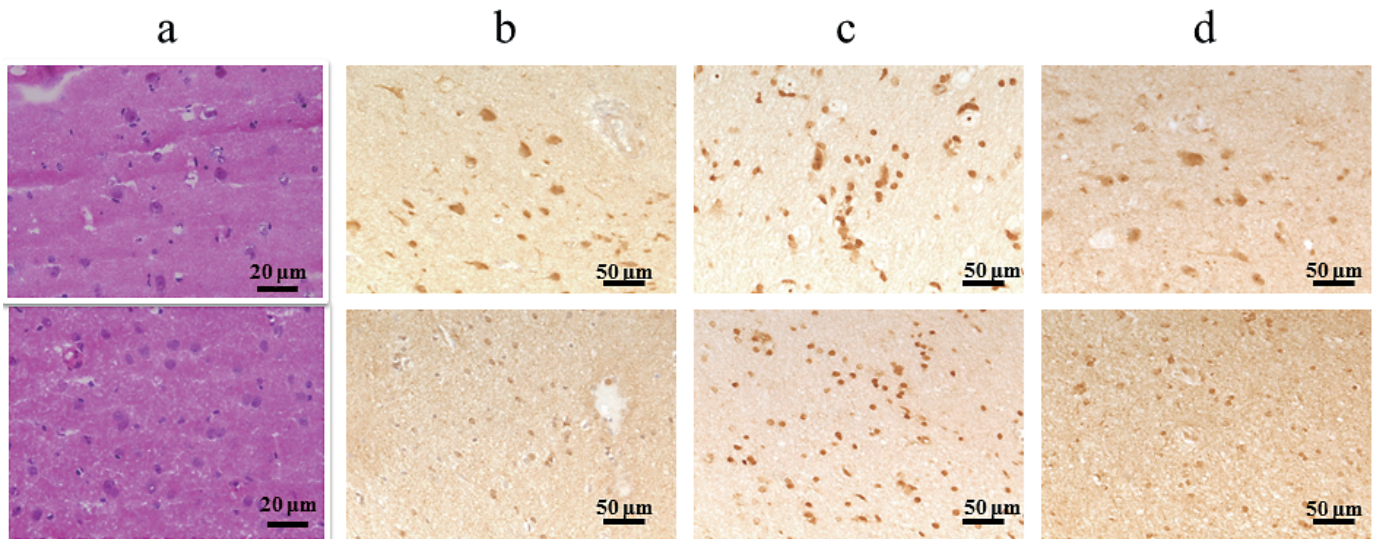


Fig. 3. Brain biopsy from the right temporal lobe. (3a) H&E stain revealed mildly increased neuroglia cells and the absence of necrosis or degeneration. However, the growth of astrocytes and intranuclear inclusion were not seen. (3b-3d) Immunostaining for JC virus (*upper*, cortex; *lower*, white matter). Agno C (3b) was mainly positive in neuronal cell bodies; VP1BC (3c) was positive in nuclei, and bodies of neuronal cells and neuroglia cells; and VP2 (3d) was positive in nuclei, bodies of neuronal cells, and bodies of neuroglia cells.

the patient started to have remittent fever, when multiple mass lesions in the midbrain and the right thalamus were revealed by brain MRI and computed tomography examinations (Fig. 5a). The MRI lesions were enhanced by gadolinium-containing contrast agent. A second brain biopsy was indicated, but it could not be performed because the prolonged activated partial thromboplastin time was not normalized, even after the administration of factor VIII. Laboratory data showed normal lactase dehydrogenase, increased soluble interleukin-2 receptor 747 U/mL, negative EBV viral load, and negative anti-toxoplasma IgG. There was no lymphadenopathy. The diagnosis of PCNSL was made based on the MRI and computed tomography findings, as well as the patient's underlying condition.

Since independent breathing had become difficult, the patient was put on a mechanical ventilator in March 2013. He responded to four doses of rituximab (375 mg/m² i.v. weekly) (Fig. 5b), supporting the diagnosis of PCNSL. In July, the mass lesions in the brain became enlarged again and did not respond to another rituximab therapy. He died as a result of whole-brain death in September 2013.

Macroscopic findings of the autopsied specimen revealed broad severe degeneration in the cerebrum and brain stem

(Fig. 6a). The infiltration of lymphoid cells was only observed in the remaining tissues around the Virchow-Robin space (Fig. 6b). The size of the lymphoid cells ranged from medium to large, and immunohistochemistry showed that those cells were CD45 (LCA)-positive, CD20-positive, CD3-negative, and EBV-encoded small RNA-1-negative (Fig. 6c, 6d). Clonality analysis of the specimen revealed the rearrangement of immunoglobulin heavy chain (Fig. 7). B-cell malignant lymphoma was confirmed, but findings of PML were not seen.

DISCUSSION

There are several atypical findings that could challenge our clinical diagnosis of PML. First, HIV-related PML usually occurs when CD4-positive T cells are severely suppressed.⁴ However, PML may also develop in patients with blood CD4-positive T-cell counts of no less than 200 cells/ μ L after the initiating ART, or in those without previous immunomodulatory drugs or immunosuppression, while the latter would be the case much more rarely.⁵⁻⁷ Hence, the relatively high number of CD4-positive T cells in the present case does not rule out the diagnosis of PML. Secondly, the

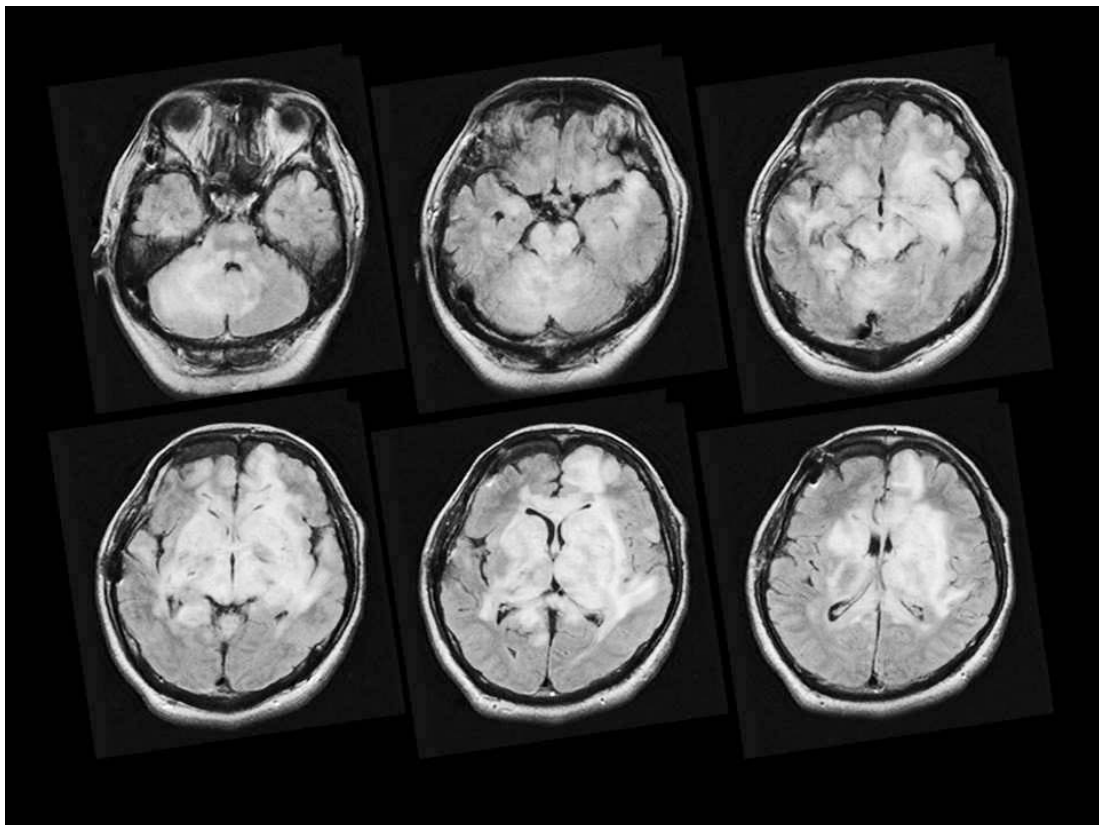


Fig. 4. Magnetic resonance imaging in September 2012. The lesions of the bilateral white matter and the left frontal cortex deteriorated.

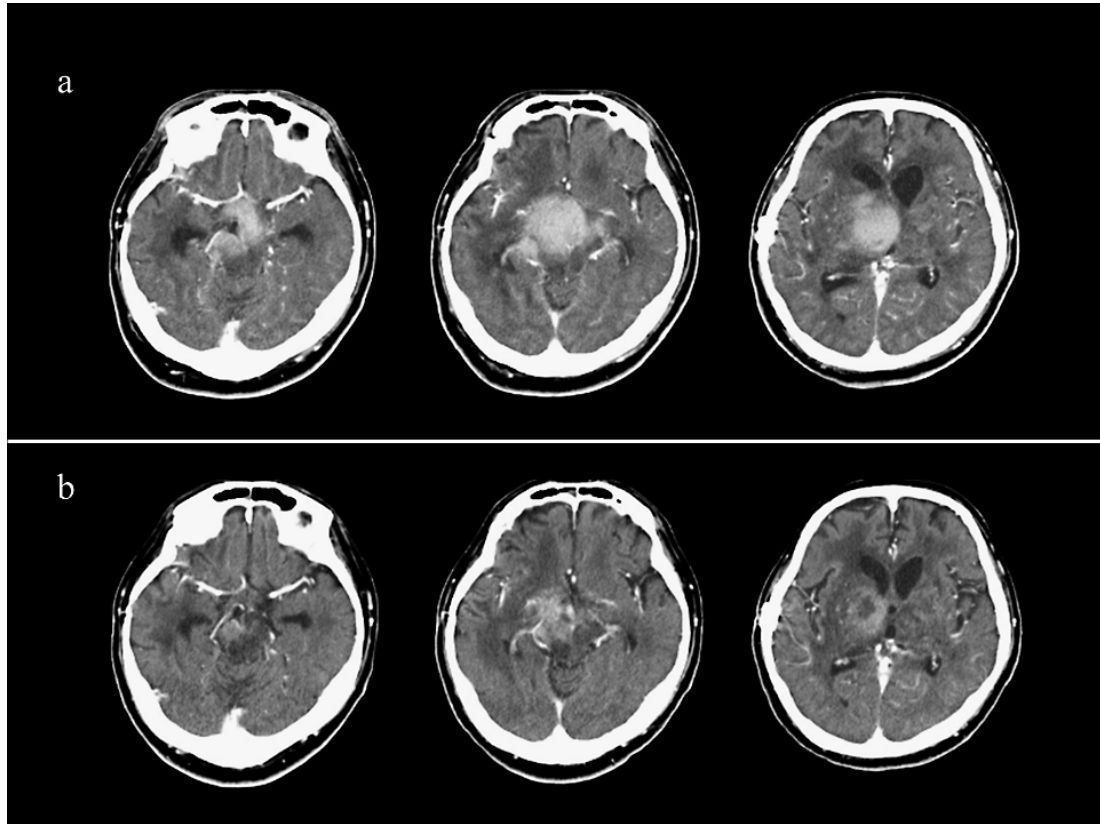


Fig. 5. Enhanced computed tomography showed multiple mass lesions. (*5a*) (upper) In March 2013, before rituximab treatment. (*5b*) (lower) In April 2013, after rituximab treatment (375 mg/m², weekly, four courses). The reduced mass was accompanied by necrosis inside.

absence of JCV in CSF and the lack of glial reaction in the tissue of brain biopsy in the present case could be misleading. The rate of positive detection of JCV in CSF is known to be reduced in the ART era.⁸ Moreover, atypical findings of brain biopsy might be attributable to the administration of mefloquine or mPSL. According to the diagnostic criteria of PML, issued by the Ministry of Health, Labour and Welfare, Japan, the present case was classified clinically into possible PML.

The use of combined antiretroviral therapy markedly improves immune function and prognosis in HIV-infected patients.⁹ However, PML may develop or worsen with antiretroviral therapy, in spite of a recovery of the immune system.¹⁰⁻¹² Immune reconstitution following initiation of combined antiretroviral therapy may lead to activation of an inflammatory response, that is, immune reconstitution inflammatory syndrome (IRIS), to detectable or latent JCV infection.¹³ Although it was reported that PML-IRIS developed between 1 week and 26 months after initiation of antiretroviral therapy,¹³ it took almost 5 years to develop PML after improvement of the patient's adherence followed by the substantial reduction in VL in the present case. As the increase

in the count of CD4-positive lymphocytes after the VL reduction was small, as shown in Fig. 1, the inflammatory response due to the immune reconstitution seemed to be weak. Therefore, the effect of IRIS on the development of PML might have been small in the present case.

The favorable response to rituximab as well as autopsy findings supports the diagnosis of PCNSL. While EBV is almost exclusively positive in PCNSL associated with HIV infection,¹⁴ the association of EBV was not demonstrated in the present case. B lymphocytes are known to be a potential site for latent infection and reactivation of JCV,^{1,15,16} and a potential role of the virus in the pathogenesis of PCNSL was previously proposed.^{17,18} The present case exhibited JCV-positive PCNSL with HIV infection complicated with possible PML, although the oncogenicity of the JCV was not proven, unlike in a previous case reported by Gallia *et al.*¹⁷

The standard therapy for PCNSL associated with HIV infection has yet to be determined. PML patients are usually unlikely to be candidates for high-intensity chemotherapies. Therefore, rituximab therapy might be a choice of treatment for patients with a poor general condition. The median survival is said to be 1.8 years for those with HIV-related PML,¹⁹

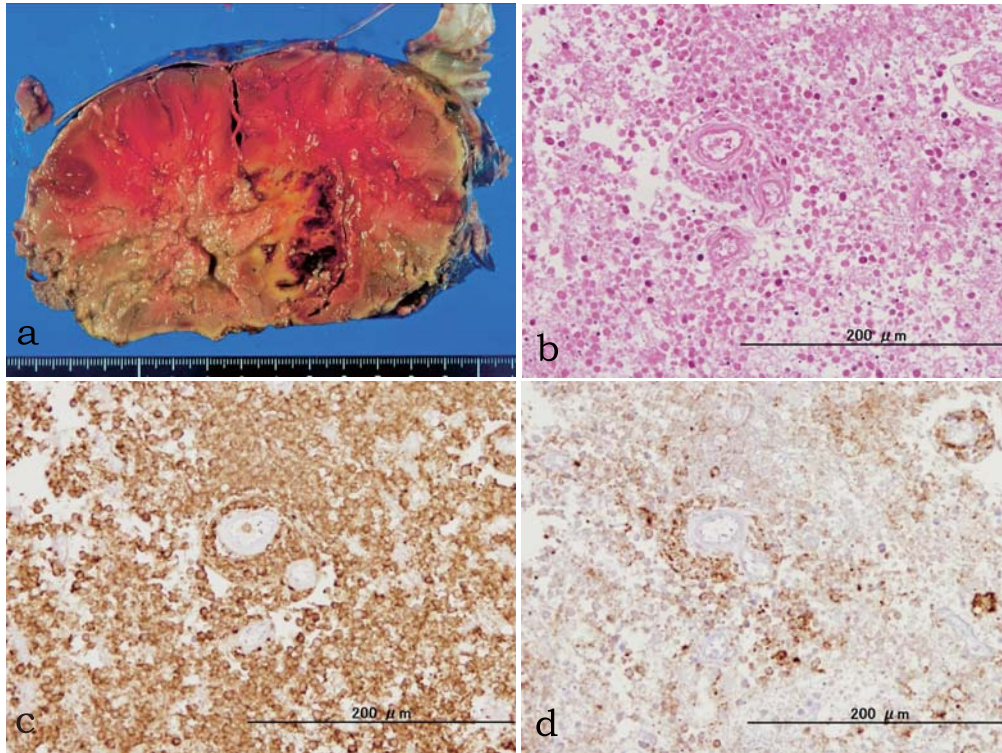


Fig. 6. Autopsy findings. (*6a*) Macroscopic findings of the brain. It was highly necrotized throughout. (*6b*) H&E stain. Lymphoid cell infiltration was seen in the remaining tissue around Virchow-Robin space. The size of the lymphoid cells was medium or large. (*6c*, *6d*) Immunostaining. CD45 (LCA) (*6c*) and CD20 (*6d*) were positive in lymphoid cells.



Fig. 7. Semi-nested polymerase chain reaction in the region of IgH CDR III. Genetic reconstitution was affirmed. *Far left lane*, molecular size markers: 100 bp DNA ladder; *lane 1*, present patient; *lane 2*, positive control; *lane 3*, negative control.

and 0.2 years for those with HIV-related PCNSL.²⁰ Thus, the extremely poor outcome of our patient could be attributable to PCNSL complicated with JCV infection, which indicates the urgent need to develop more effective therapy for PCNSL with concomitant infection of JCV during the course of HIV infection.

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CONFLICT OF INTEREST

The authors declare no competing financial interests.

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