

[ CASE REPORT ]

## An Adult Case of Herpes Simplex Virus-associated Granulomatous Encephalitis

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### Abstract:

Brain granuloma occurs under certain conditions. Herpes simplex virus (HSV) causes granulomatous encephalitis in children; however, it has been rarely reported in adults. A 74-year-old man with a history of herpes simplex encephalitis suffered recurrent seizures. Brain magnetic resonance imaging revealed a mass lesion and resection was performed. A polymerase chain reaction using a brain biopsy specimen was positive for HSV DNA; thus, the patient was diagnosed with HSV-associated granulomatous encephalitis. After administering acyclovir, the patient showed improvement. HSV can cause granulomatous encephalitis in adults, and acyclovir can be used for its treatment.

**Key words:** granulomatous encephalitis, herpes simplex virus, reactivation, adult, acyclovir

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### Introduction

Brain granuloma has been reported to occur in tuberculosis or fungal infection, sarcoidosis, and granulomatous vasculitis (1). Although uncommon, herpes simplex virus (HSV) has been reported to cause granulomatous encephalitis in children (2-5); however, reports in adults are rare. We herein report an adult case of HSV-associated granulomatous encephalitis, which was successfully treated with acyclovir alone.

### Case Report

A 58-year-old man who presented with fever, left complex partial seizure, and disturbed consciousness was admitted to our hospital. The right amygdala and hippocampus appeared hyperintense on T2-weighted magnetic resonance imaging (MRI) of the brain. A cerebrospinal fluid (CSF) examination indicated mild lymphocytic pleocytosis and elevated protein levels. We also noted a positive HSV IgM titer and a significant increase ( $<0.20$ - $12.80$ ) in the HSV IgG

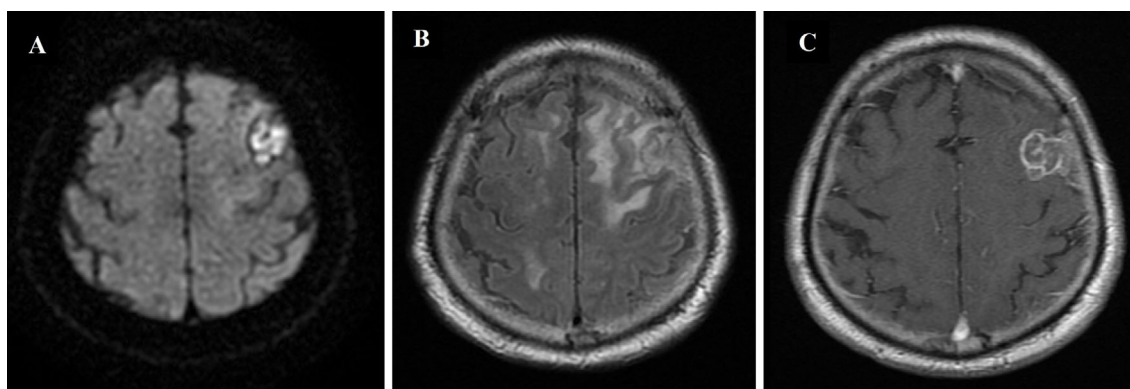
titer with paired CSF. Based on these findings, the patient was diagnosed with herpes simplex encephalitis (HSE), and was treated with acyclovir (500 mg, three times daily) for 16 days. The patient recovered and was discharged with a prescription for antiepileptic drugs.

At 74 years of age, the patient suffered a right complex partial seizure and was hospitalized. He presented with atrial fibrillation and was treated with anticoagulant drugs. He also had mild diabetes mellitus (glycated hemoglobin, 6.7%) but his blood glucose level was controlled with diet therapy. He did not have human immunodeficiency virus infection and was not undergoing treatment with steroids or immune-suppressing drugs. His serum IgG level was normal. Electroencephalography revealed left epileptic discharge in the left frontal region. We increased the dosage of antiepileptic drugs, and the patient's seizures were controlled. A CSF analysis revealed mild lymphocytic pleocytosis, but the protein and glucose levels were normal. MRI revealed a mass lesion in the left frontal lobe, which showed no gadolinium enhancement and which was hypointense on T2 star-weighted imaging. We therefore considered the mass lesion to be a hemorrhage. The mass lesion gradually became en-

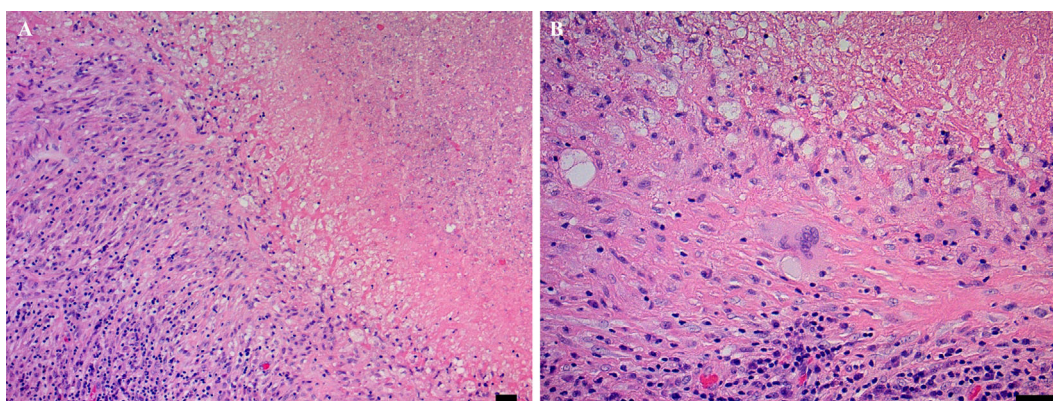
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**Figure 1.** Brain magnetic resonance imaging (MRI) on the third admission. (A) A diffusion-weighted image showing a high signal in the left frontal lobe. (B) Fluid attenuated inversion recovery showing a high signal with mild perifocal edema in the left frontal lobe. There was no obvious white matter involvement. (C) T1-weighted post-gadolinium MRI showing ring enhancement of the mass in the left frontal lobe. The mass lesion was present at the same location on MRI as on the second admission.



**Figure 2.** The brain biopsy findings. (A) 20-power view showing necrotic tissue surrounded by epithelioid cells, foamy cells and a few multinucleated giant cells indicating necrotic granuloma, with lymphocytes and plasma cell infiltration [Hematoxylin and Eosin (H&E) staining]. (B) A 40-power view showing the same findings (H&E staining). Both scale bars: 10  $\mu$ m

larged, and perifocal edema progressed. As the brain lesion became enlarged, the patient suffered from drowsiness. After we reduced the dosage of anticoagulant drugs, there was no further enlargement of the mass and the perifocal edema decreased. The patient was discharged with mild cognitive dysfunction and aphasia.

Approximately 3 months later, the right complex partial seizures recurred and he was hospitalized for the third time. We changed his antiepileptic drugs, which controlled his seizures. A CSF examination was normal. MRI revealed an expanded mass lesion with ring enhancement in the left frontal lobe. The mass showed little perifocal edema (Fig. 1). We suspected a brain tumor and performed resection. A pathological examination revealed necrotic granuloma with lymphocytes and plasma cells (Fig. 2). There was little fibrosis caused by granuloma, but it was not considered to be a brain scar from past HSE. Microbiological tests for bacteria, tuberculosis, and fungi were negative. There were no findings suggestive of sarcoidosis or granulomatous vasculitis. There were no viral inclusions; however, a polymerase chain

reaction (PCR) using a frozen brain biopsy specimen was positive for HSV DNA; thus, we diagnosed the patient with HSV-associated granulomatous encephalitis. Immunohistochemistry for HSV-1 and HSV-2 revealed nonspecific findings and was considered to be negative. We could not test for the presence of HSV DNA in the CSF using a PCR pre-operatively; however, the PCR results were negative on post-operative day 17. To assess the HSV activity, we retrospectively measured the HSV IgG titer in the CSF. The HSV IgG titer, which was measured using an enzyme immunoassay, was 2.40 at the second admission and increased to 13.30 just before surgery. The HSV titer was elevated in HSV-1 but not HSV-2. Thus, we suspected HSV reactivation and administered acyclovir (500 mg twice daily; reduced according to the renal function) for 21 days. After acyclovir treatment, the CSF HSV IgG titer decreased to 2.80. The patient was discharged with moderate cognitive dysfunction and mild aphasia; however, he was able to perform activities of daily living independently. The seizures and cerebral mass have not recurred during 10 months of follow-up.

**Table. Comparison of Herpes Simplex Granulomatous Encephalitis in Adult Patients.**

	Ref. 6 (case 1)	Ref. 6 (case2)	Current case
age	55	54	74
sex	female	female	male
previous disease	multiple sclerosis (not used disease-modifying treatments)		herpes simplex encephalitis
symptom	dysphagia, disturbance of consciousness	fever, headache, disturbance of consciousness, epilepsy	epilepsy
HSV DNA PCR in CSF	-	-	-
HSV IgG in CSF	elevated (HSV-1)	elevated (HSV-1)	elevated (HSV-1)
HSV DNA PCR in brain tissue	+	+	+
HSV immunohistochemistry	-		-
treatment & course	deteriorated with acyclovir improved with steroid	deteriorated with acyclovir and valacyclovir improved with steroid	improved with acyclovir

HSV: herpes simplex virus, PCR: polymerase chain reaction, CSF: cerebrospinal fluid

## Discussion

This case provides two important suggestions for clinical practice. First, although rare, HSV can cause granulomatous encephalitis in adults. None of the reported adult cases had immunosuppressive diseases or drugs, suggesting that HSV-associated granulomatous encephalitis also occurs in immunocompetent adults. This therapeutic opportunity should not be overlooked. There are several reports on HSV-associated granulomatous encephalitis in children (2-5), and the clinical features included intractable epilepsy, progressive neurological deficits, and in almost all of the cases: a history of HSE. In most cases, HSV DNA is not detected in the CSF. Hence, the detection of HSV DNA in brain tissue and the results of immunochemical staining were important clues for the diagnosis. As described above, a few cases of HSV-associated granulomatous encephalitis have been reported in adults (6). Table compares our case to the previous cases. In all adult cases, the virus type was HSV-1. The clinical features in adults were similar to those observed in children; however, a past history of HSE was only noted in our case. HSV has been reported to persist for long durations in human brain tissue following encephalitis (7, 8) and recurrent HSE in adults (9). Thus, in cases of brain granuloma, it is important to test for HSV reactivation, particularly if the patient has a history of HSE. HSV DNA was not detected in the patient's CSF; however, the CSF HSV IgG titer was elevated in all cases. The detection of HSV IgG in CSF may be a useful screening tool for HSV-associated granulomatous encephalitis.

Second, acyclovir was effective for HSV-associated granulomatous encephalitis in our patient. After acyclovir treatment, the CSF HSV IgG titer was significantly decreased, and the patient had no recurrence of the cerebral mass for 10 months after treatment. Acyclovir has been reported to be effective in children (2, 4). However, two reported adult cases showed a poor response to acyclovir and improved

with corticosteroid treatment (6). We believe that this difference could be due to differences in the main etiology, viral reactivation, and the immune reaction to infection. Spiegel et al. suggested that both postinfectious immunoinflammatory reaction and viral reactivation, which resulted in a late relapse of HSE in children (10), and HSV-associated granulomatous encephalitis may occur by a similar mechanism. They also reported that virus reactivation caused cortical lesions. Conversely, an immunoinflammatory reaction led to diffuse white matter involvement and cerebral edema. In cases reported by Varatharaj et al., an immune reaction to HSV infection was believed to have been the main mechanism underlying the development of HSV-associated granulomatous encephalitis (6). In fact, the two reported cases showed greater white matter involvement and cerebral edema than our patient, suggesting a stronger immune response to infection. The immunoinflammation may mask the therapeutic effect of acyclovir. HSV-associated granulomatous encephalitis may occur with viral infection and the immune response to infection. Acyclovir is effective against the viral infection, whereas corticosteroids may be required for patients with a strong immune response. Acyclovir is necessary for HSV-associated granulomatous encephalitis because HSV infection or reactivation must be present, regardless of the degree of immune response.

The reason behind the dissociation between the HSV DNA and immunohistochemistry findings remains unclear. Similar dissociation was also reported in cases involving children and adults (4, 6). The lower sensitivity of immunohistochemistry may lead to false negative results.

Total resection of granuloma may have improved the status of our case. In fact, Love et al. reported a case of a child with HSV-associated granulomatous encephalitis who showed improvement following hemispherectomy without the administration of acyclovir (3). It remains unclear whether the administration of acyclovir was necessary after the total resection of the granuloma; however, it was appropriate to administer acyclovir because reactivated HSV may

remain at other brain sites. Further research is needed to resolve this question.

In conclusion, HSV can cause granulomatous encephalitis in adults, and acyclovir can be effective for its treatment. As there are few reports of HSV causing brain granuloma in adults, the condition may go undiagnosed. Thus, when the cause of brain granuloma is unknown, the possibility of HSV infection should be considered, especially in patients whose CSF shows a high HSV IgG titer or patients with a history of HSE. HSV-associated granulomatous encephalitis can be treated with acyclovir; however, some patients require additional corticosteroids. Further research is required to identify the best course of treatment.

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

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