

[CASE REPORT]

An Autopsy Case of Varicella Zoster Virus Encephalitis with Multiple Brain Lesions

Tomohiro Suzuki¹, Syuichi Tetsuka¹, Tomoko Ogawa¹, Ritsuo Hashimoto¹,
Shinya Okada² and Hiroyuki Kato¹

Abstract:

Varicella-zoster virus (VZV) encephalitis in the absence of vasculopathy may rarely occur in association with herpes zoster. We herein report the case of a 67-year-old woman with non-Hodgkin's lymphoma undergoing chemotherapy who presented with an acute alteration in consciousness. Magnetic resonance imaging of the brain revealed multiple and nonspecific lesions of hyperintensity with mild edema in the cortex and sub-cortex. She was treated with intravenous acyclovir. However, two days after admission, the patient died and was diagnosed with VZV encephalitis. This case highlights the risk of VZV reactivation with severe neurological complications in patients undergoing immunosuppressive therapy.

Key words: varicella-zoster virus, encephalitis, histopathology

(Intern Med 59: 1643-1647, 2020)

(DOI: 10.2169/internalmedicine.3417-19)

Introduction

Varicella-zoster virus (VZV) infection may cause various neurologic signs and symptoms; however, central nervous system complications are considered rare (1-3). Owing to improvements in the diagnostic techniques through the introduction of polymerase chain reaction (PCR), the ability to identify the virus in VZV encephalitis has increased.

VZV encephalitis is caused by the reactivation of latent VZV infecting the ganglia. Background factors include immune abnormalities, herpes zoster in the head and neck area, and disseminated herpes zoster. If reactivation occurs more than once, encephalitis is considered to be a common diagnosis (4). The mortality rate is approximately 10%, and patients with VZV encephalitis who are immunodeficient often have particularly severe sequelae (5).

We herein report the clinical course of a woman who developed VZV encephalitis following herpes zoster reactivation during chemotherapy for lymphoma. She died in a short time despite treatment with acyclovir.

Case Report

A 67-year-old woman with non-Hodgkin's lymphoma was treated with 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP). While approaching her last cycle of chemotherapy, she noticed a cutaneous rash accompanied by blisters in her right occipital region seven days before admission. From five days before admission, she complained of nausea and vomiting. She was admitted to our hospital because her complaints worsened, and she was unable to eat anything.

On admission, her temperature was 36.9°C, heart rate 70 beats/min, SaO₂ 99%, and blood pressure 120/84 mmHg. A neurologic examination revealed the following: a mildly decreased level of consciousness (Glasgow coma scale score of 12, E3V4M5), able to answer simple questions but unable to follow detailed instructions; and restless behavior and unable to sustain attention. Her tendon reflexes were slightly enhanced in the right upper and lower limbs, and Babinski's sign was positive on the right. There was no muscle atrophy, and the muscle tone was normal. There was no neck stiffness.

¹Department of Neurology, International University of Health and Welfare Hospital, Japan and ²Department of Pathology, International University of Health and Welfare Hospital, Japan

Received: June 7, 2019; Accepted: February 2, 2020; Advance Publication by J-STAGE: April 2, 2020

Correspondence to Dr. Tomohiro Suzuki, tomohiro@iuhw.ac.jp,

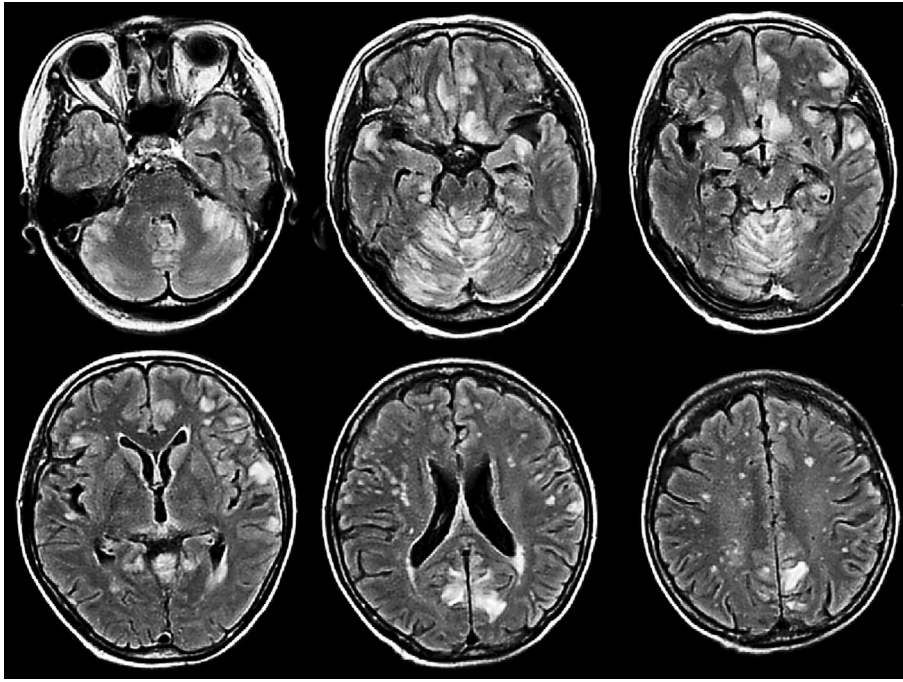


Figure 1. Magnetic resonance imaging (MRI) of the brain on fluid-attenuated inversion recovery sequence. MRI revealed multiple and nonspecific lesions of hyperintensity with mild edema in the cortex and subcortex of the cerebrum and cerebellum.

Magnetic resonance imaging (MRI) of the brain on a fluid-attenuated inversion recovery sequence revealed multiple nonspecific hyperintense lesions with mild edema in the cortex and subcortex of the cerebrum and cerebellum (Fig. 1). These abnormal findings were not seen on diffusion- or T1-weighted images, nor did they show enhancement on gadolinium-enhanced T1-weighted images. Magnetic resonance angiography did not reveal vascular abnormalities. Lumbar puncture was performed, and the opening pressure was 19.5 cmH₂O. A cerebrospinal fluid (CSF) analysis showed leukocytic pleocytosis (984 cells/mm³, 92% leukocytes) with elevated protein (1,237 mg/dL) and normal glucose levels (89 mg/dL, blood glucose ratio 61.8%). The initial CSF Gram stain was negative, and microbial culture showed no growth.

Because we suspected a viral cause for the patient's encephalitis, intravenous acyclovir (10 mg/kg, every 8 h) was initiated as empirical treatment while we awaited the results of further diagnostic tests. One day later, the patient developed delirium. Her mental status worsened, and she eventually fell into a coma. Two days after admission, Cheyne-Stokes respiration appeared from around 5 am. A dilated right pupil with absent reaction to light was noted. Spontaneous breathing stopped around 8 am, and she died.

Viral studies by polymerase chain reaction (PCR) revealed the presence of VZV DNA in both the CSF and serum but no evidence of herpes simplex virus. In addition, no malignant cells were detected in the CSF. The concomitant presence of encephalitis and non-Hodgkin's lymphoma in the presence of VZV DNA in the CSF led to the diagnosis of VZV encephalitis. An autopsy was performed with the con-

sent of the family 48 h after death.

Autopsy Findings

Upon a gross autopsy examination, the fresh brain weighed 1,368 g. There was evidence of brain edema and herniation (Fig. 2). Varicella-zoster infection can be identified microscopically by the presence of multinucleated cells with ground-glass, slate to steel-gray nuclear inclusions with irregular chromatin margination. Viral inclusions such as those were identified in specimens from the temporal skin rash (Fig. 3). A neuropathology examination of hematoxylin and eosin-stained histologic sections of the cerebral cortex demonstrated multiple inflammatory foci in the Virchow-Robin space, primarily infiltrates of neutrophils and histiocytes (Fig. 4). There was no evidence of viral inclusions in tissue from the brain itself or the spinal cord. A collection of leukocytes, mainly neutrophils, was observed in the blood vessels of the cerebral cortex, but only edema was seen in the cerebral white matter where high-intensity MRI signals had been seen, suggesting inflammation. No leukocytic infiltrate of blood vessels was seen. In addition, the histopathology findings did not reveal multifocal vasculopathy.

Discussion

We encountered an immunocompromised adult who presented with acute alteration in the level of consciousness, a cutaneous rash, and virologic evidence of VZV in the serum and CSF. Although VZV encephalitis is rare in immunocompromised patients, it is mainly described in those with severe immunocompromise, such as patients undergoing treat-

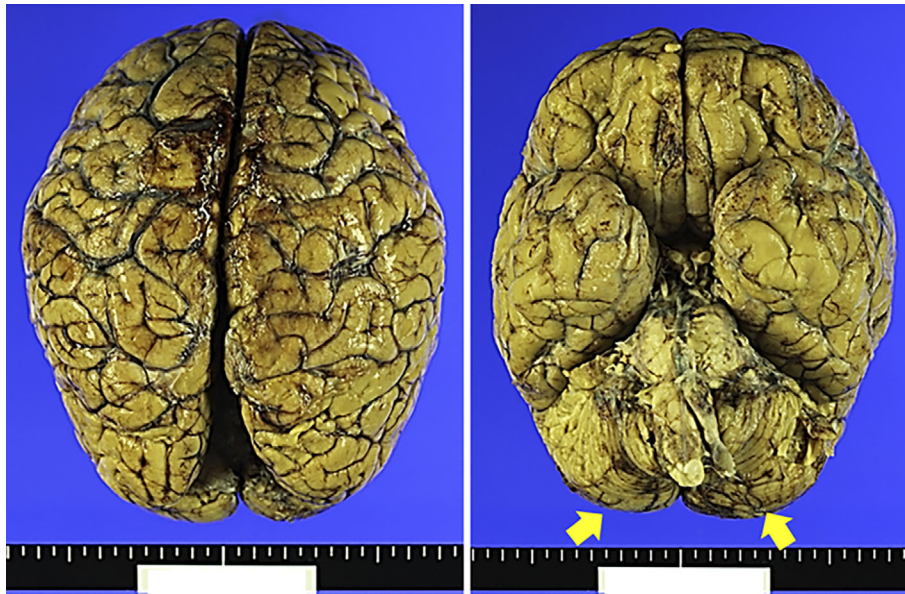


Figure 2. Macroscopic findings of brain. Flattening of the gyrus and indentation around the foramen magnum were recognized, which indicated brain edema and herniation.

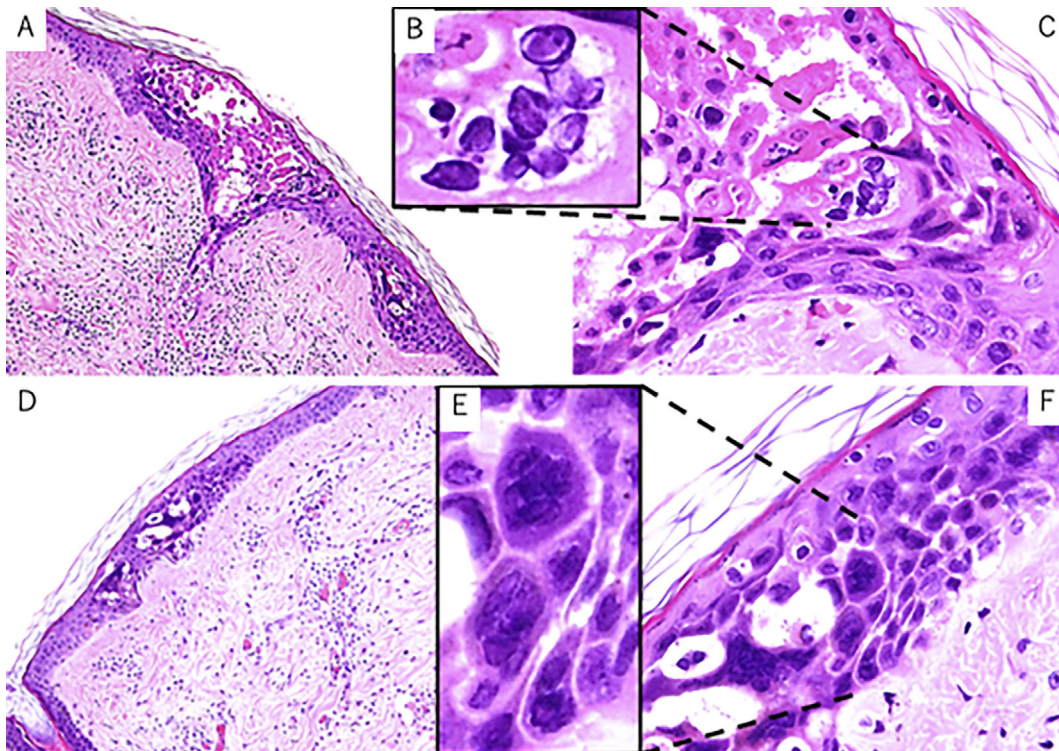


Figure 3. Pathological findings of the skin. Histologically, a higher magnification of the Varicella-Zoster inclusions showed multinucleation with back-to-back ground-glass, slate to steel-gray, nuclear inclusions with chromatin margination (A and D $\times 100$, B and E $\times 1000$, C and F $\times 400$).

ment for nonsolid malignancies, as in the present case (6). In 2 large retrospective cohort studies, the incidence of herpes zoster varied by type of cancer, with 31 cases per 1,000-person years in patients with hematologic malignancies (7). The risk of herpes zoster in patients with malignant lymphoma was 8.23 times higher than that in control patients (8). The incidence of and hazard ratios for herpes zoster in patients with hematologic malignancies, such as

malignant lymphoma, are high compared with those in patients with solid cancers (7, 8). The overall incidence of herpes zoster has been reported to be 12.21% in patients with non-Hodgkin's lymphoma, 11.79% in those receiving conventional chemotherapy, and 12.76% in those receiving rituximab-containing chemotherapy (9). Most herpes zoster episodes occurred within the first two years after the diagnosis of non-Hodgkin's lymphoma. In addition, the incorpora-

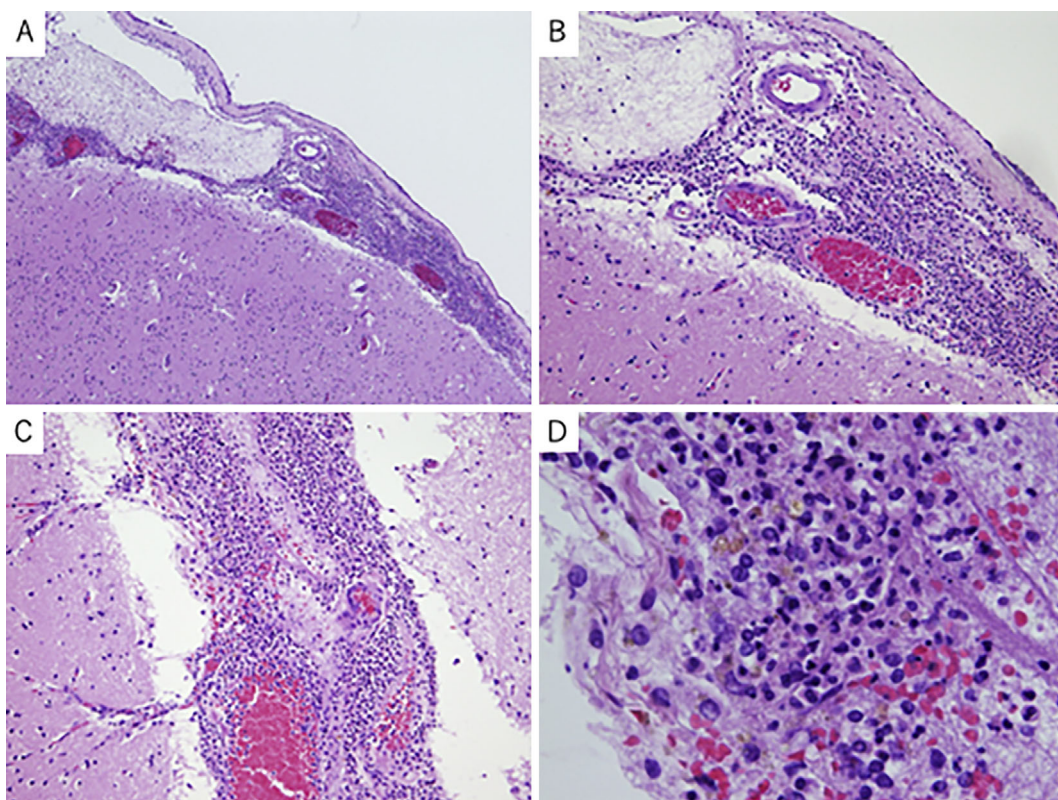


Figure 4. Neuropathological findings of the brain. There were multiple foci of inflammatory cells in the Virchow-Robin space, and the inflammatory cells mainly comprised neutrophils and histiocytes in the cerebral cortex (A $\times 40$, B and C $\times 200$, D $\times 1000$).

tion of rituximab in conventional chemotherapy regimens was associated with an increased short-term risk of herpes zoster (9). Based on these facts, it is highly likely that the patient in this case suffered from herpes zoster that progressed to VZV encephalitis.

VZV encephalitis is characterized by delirium presenting within a variable period preceding or following eruption of a cutaneous zoster rash. The proportion of VZV encephalitis cases in which a rash was found is reported to be 55% to 62% (10, 11). In the present case, the rash was noted first, and progressive neurologic signs appeared thereafter. The diagnosis of VZV encephalitis is important because the prognosis of encephalitis is poorer than that of VZV meningitis (11). To our knowledge, compared with more common lesions, such as gray-white matter junction lesions that indicate small vessel arteriopathy (11), multiple, nonspecific lesions in both the cortex and subcortex of the cerebrum and cerebellum are extremely rare. Three mechanisms have been proposed for the pathophysiology of VZV encephalitis: demyelinating disease, vasculopathy, and acute infectious encephalitis of unconfirmed pathophysiology (6). However, there have so far been few reports on the viral and pathological findings of VZV encephalitis (1, 2). The most likely pathophysiology in this case was direct infection of glial cells as an acute infectious encephalitis (12), as MRI revealed multiple, nonspecific lesions in both the cortex and subcortex of the cerebrum and cerebellum. Although some cases of VZV encephalitis may actually be a vasculopa-

thy (13), encephalitis in the absence of vasculopathy may rarely occur in association with herpes zoster (14). Multiple lesions mimicking metastatic cancer in the brain may be a rare manifestation of viral encephalitis. Thus far, reports have shown herpes simplex virus (15, 16), Epstein-Barr virus (17, 18), and VZV (19) encephalitis presenting as a brain tumor or brain tumor progression (20, 21).

The diagnosis of VZV encephalitis may be established using PCR to detect VZV DNA in the CSF. However, the isolation or detection of VZV in a CSF specimen is relatively uncommon, due to the fact that the presence of the virus is closely linked to the timing of the CSF collection in the course of a CNS viral infection (22). Therefore, empirical treatment with acyclovir (10 mg/kg intravenously every 8 h) for possible HSV-1 infection should be started as soon as possible in cases of encephalitis without a clear etiology (23). Early treatment is important because it is associated with a significant reduction in mortality and morbidity. In the case presented here, the administration of acyclovir was initiated as soon as possible when encephalitis was suspected, but the patient unfortunately could not be saved.

The present case highlights the risk of VZV reactivation with severe neurologic complications in patients undergoing immunosuppressive therapy. In our case, a pathological examination of the multifocal lesions seen on MRI showed only edema without inflammation. We considered the possibility of immunosuppression causing a poor inflammatory response, but the cerebral cortex had a collection of leuko-

cytes, primarily neutrophils, as seen in meningitis, suggesting that possibility to be unlikely. The pathological findings of VZV encephalitis are poorly reported, and the accumulation of more cases is necessary.

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

References

- Bucci FA Jr, Schwartz RA. Neurologic complications of herpes zoster. *Am Fam Physician* **37**: 185-192, 1988.
- Thomas JE, Howard FM Jr. Segmental zoster paresis—a disease profile. *Neurology* **22**: 459-466, 1972.
- Hughes BA, Kimmel DW, Aksamit AJ. Herpes zoster-associated meningoencephalitis in patients with systemic cancer. *Mayo Clin Proc* **68**: 652-655, 1993.
- Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis* **44** (Suppl): S1-S26, 2007.
- Kleinschmidt-DeMasters BK, Amlie-Lefond C, Gilden DH. The patterns of varicella zoster virus encephalitis. *Hum Pathol* **27**: 927-938, 1996.
- De Broucker T, Mailles A, Chabrier S, Morand P, Stahl JP; Steering Committee and Investigators Group. Acute varicella zoster encephalitis without evidence of primary vasculopathy in a case-series of 20 patients. *Clin Microbiol Infect* **18**: 808-819, 2012.
- Habel LA, Ray GT, Silverberg MJ, et al. The epidemiology of herpes zoster in patients with newly diagnosed cancer. *Cancer Epidemiol Biomarkers Prev* **22**: 82-90, 2013.
- Hata A, Kuniyoshi M, Ohkusa Y. Risk of herpes zoster in patients with underlying diseases: a retrospective hospital-based cohort study. *Infection* **39**: 537-544, 2011.
- Cho SF, Wu WH, Yang YH, Liu YC, Hsiao HH, Chang CS. Longitudinal risk of herpes zoster in patients with non-Hodgkin lymphoma receiving chemotherapy: a nationwide population-based study. *Sci Rep* **5**: 14008, 2015.
- Hokkanen L, Launes J, Poutiainen E, et al. Subcortical type cognitive impairment in herpes zoster encephalitis. *J Neurol* **244**: 239-245, 1997.
- Nagel MA, Cohrs RJ, Mahalingam R, et al. The varicella zoster virus vasculopathies: clinical, CSF, imaging, and virologic features. *Neurology* **70**: 853-860, 2008.
- Kleinschmidt-DeMasters BK, Gilden DH. Varicella-zoster virus infections of the nervous system: clinical and pathologic correlates. *Arch Pathol Lab Med* **125**: 770-780, 2001.
- Gilden D, Nagel MA, Cohrs RJ. Varicella-zoster. *Handb Clin Neurol* **123**: 265-283, 2014.
- Kennedy PGE, Gershon AA. Clinical features of varicella-zoster virus infection. *Viruses* **10**: 609, 2018.
- Rose JW, Stroop WG, Matsuo F, Henkel J. Atypical herpes simplex encephalitis: clinical, virologic, and neuropathologic evaluation. *Neurology* **42**: 1809-1812, 1992.
- Fiol M, Mora A, Cervio A, et al. Brain tumor or infectious disease? *Arq Neuropsiquiatr* **67**: 302-304, 2009.
- Angelini L, Bugiani M, Zibordi F, Cinque P, Bizzi A. Brainstem encephalitis resulting from Epstein-Barr virus mimicking an infiltrating tumor in a child. *Pediatr Neurol* **22**: 130-132, 2000.
- Khalil M, Enzinger C, Wallner-Blazek M, et al. Epstein-Barr virus encephalitis presenting with a tumor-like lesion in an immunosuppressed transplant recipient. *J Neurovirol* **14**: 574-578, 2008.
- Schmidt E, Yonaty SA, Jubelt B, Latorre JG. Multiple enhancing brain mass as initial presentation of varicella zoster virus encephalitis. *Austin J Clin Neurol* **3**: 1088, 2016.
- Lins H, Kanakis D, Heinrichs T, Dietzmann K, Wallesch CW, Mawrin C. Sudden progression of a glioblastoma in partial remission? *Clin Neurol Neurosurg* **106**: 335-336, 2004.
- Perez-Saldana MT, Vilar C, Geffner-Sclarsky D, et al. [Meningoencephalomyelitis as the initial symptom of a brain tumour mimicking encephalitis due to herpes simplex virus: a case report]. *Rev Neurol* **44**: 348-352, 2007.
- Gregoire SM, van Pesch V, Goffette S, Peeters A, Sindic CJ. Polymerase chain reaction analysis and oligoclonal antibody in the cerebrospinal fluid from 34 patients with varicella-zoster virus infection of the nervous system. *J Neurol Neurosurg Psychiatry* **77**: 938-942, 2006.
- Benson PC, Swadron SP. Empiric acyclovir is infrequently initiated in the emergency department to patients ultimately diagnosed with encephalitis. *Ann Emerg Med* **47**: 100-105, 2006.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).