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【 CASE REPORT 】

Acute Stroke Caused by Progressive Intracranial Artery Stenosis Due to Varicella Zoster Virus Vasculopathy after Chemotherapy for Malignant Lymphoma

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Abstract:
Decreased cell-mediated immunity can reactivate Varicella zoster virus (VZV), which can lead to various neurological complications, including vasculopathy. We herein report the case of a patient with acute stroke with progressive internal carotid artery stenosis due to VZV vasculopathy after chemotherapy for malignant lymphoma. Treatment for VZV vasculopathy improved the stenosis and prevented recurrent stroke. VZV vasculopathy is an important treatable cause of stroke in immunosuppressed patients.

Key words: varicella zoster virus vasculopathy, zoster, vasculitis, stroke, ischemic stroke, chemotherapy

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Introduction

Varicella zoster virus (VZV) is a highly neurotropic virus. After primary infection causing chicken pox, VZV remains latent in the cranial nerve ganglia, dorsal root ganglia, and autonomic ganglia along the entire neuraxis (1). Decreased cell-mediated immunity due to aging or immunosuppression reactivates VZV and results in various neurological complications, such as vasculopathy, as well as shingles (1). Malignant lymphoma, the most common hematologic malignancy, causes immunosuppression through either the disease itself or chemotherapy, and this sometimes results in VZV reactivation (2, 3).

We herein report the case of an acute stroke patient with progressive intracranial artery stenosis due to VZV vasculopathy after chemotherapy for malignant lymphoma.

Case Report

A 62-year-old woman with a history of follicular lymphoma was treated with chemotherapy [6 courses of bendamustine plus rituximab therapy (B-R)] and achieved complete remission. Lymphocytopenia continued after chemotherapy (Fig. 1). She developed shingles on the left buttock 5 months after the chemotherapy and was treated with amenamevir 400 mg for 7 days. Five months after the shingles, she suddenly developed transient right upper limb paralysis and arrived at our emergency room. She had no history of headache and no vascular risk factors other than dyslipidemia.

She had dark red scars in the left sacral distribution. She had no focal neurological symptoms. Her National Institutes of Health Stroke scale (NIHSS) score was 0. On a laboratory examination, the white blood cell count was 5,300/μL, and the lymphocyte count was 572/μL (Fig. 1). Serological tests other than low-density lipoprotein (LDL)-cholesterol (149 mg/dL) were normal. On immunological testing, the IgG and IgA values were low [IgG: 667 mg/dL (861-1,741 mg/dL), IgA: 51 mg/dL (93-393 mg/dL)]. Coagulation assays and autoantibodies were normal. Anti-VZV antibody and anti-cytomegalovirus (CMV) antibody showed a prior infectious pattern.

Chest X-ray, electrocardiography, and echocardiography findings were normal. Brain magnetic resonance imaging (MRI) showed a small acute cerebral infarction in the cortical region of the left frontal lobe (Fig. 2A). MR angiography (MRA) showed the loss of the blood flow signal at the top of the left internal carotid artery (ICA) (Fig. 2B), and three-dimensional (3D) rotational angiography showed se-

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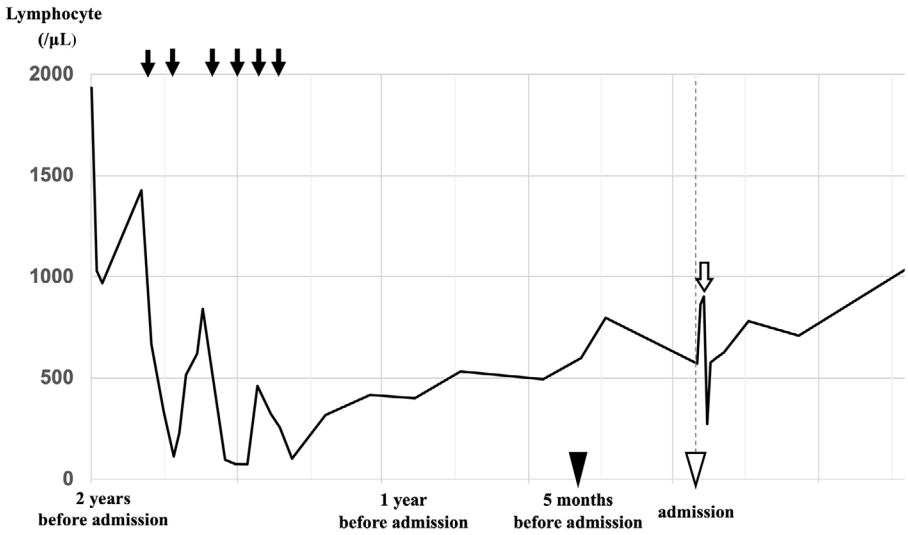

Figure 1. **Changes in the lymphocyte count. The black arrow indicates one course of bendamustine plus rituximab therapy. The white arrow indicates one course of steroid pulse therapy. The black arrowhead indicates the onset of shingles. The white arrowhead indicates the onset of varicella zoster virus vasculopathy.**

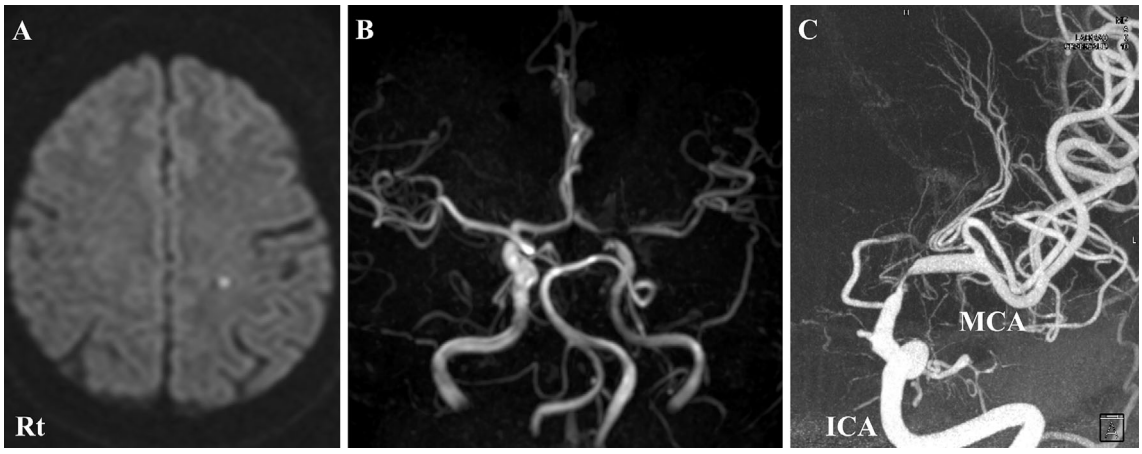

Figure 2. **Brain imaging findings. (A) MRI was performed on admission using a 1.5-T MRI scanner. Axial DWI (TR 6,000 ms, TE 100 ms, b-value 1,000 sec/mm^2) showed a small, high-intensity signal in the left middle cerebral artery (MCA) region. (B) MRA (Time of flight, TR 32 ms, TE 6.8 ms) on admission showed severe stenosis at the top of the left internal carotid artery (ICA), and the signal from the blood flow of the left MCA was lower than that of the contralateral MCA. (C) 3D-reconstruction of left ICA rotation angiography showed severe stenosis at the top of the left ICA.**

vere stenosis in the lesion (Fig. 2C). However, on contrast-enhanced CT three months before admission as follow-up for malignant lymphoma, the top of the ICA had no stenoocclusive lesions (Fig. 3A). Gadolinium-enhanced 3D black-blood T1-weighted imaging (vessel wall imaging; VWI) showed concentric vessel wall enhancement at the top of the left ICA (Fig. 3B-D). The wall enhancement index (WEI) of the stenotic lesion (4) was 2.66. Cerebrospinal fluid (CSF) analyses showed a slightly elevated protein level. Polymerase chain reaction (PCR) for VZV DNA in CSF was negative. In contrast, VZV-IgM was positive in CSF, and the anti-VZV IgG antibody index [4.17 (>2.0)] increased, which meant increasing intrathecal synthesis of anti-VZV IgG antibody. A diagnosis of acute ischemic stroke due to intracranial arterial stenosis caused by VZV vasculopathy was therefore made.

The patient was treated with oral aspirin 100 mg per day, rosuvastatin 2.5 mg per day, intravenous acyclovir 10 mg/kg every 8 hours for 4 days, and oral prednisone 1 mg/kg for 5 days. Despite these therapies, MRI at 17 days after admission showed recurrence of asymptomatic cerebral infarction in the left ICA region. Intravenous methylprednisolone 1,000 mg per day was then given for 3 days, and the dosage of aspirin was increased to 200 mg per day. She then had no

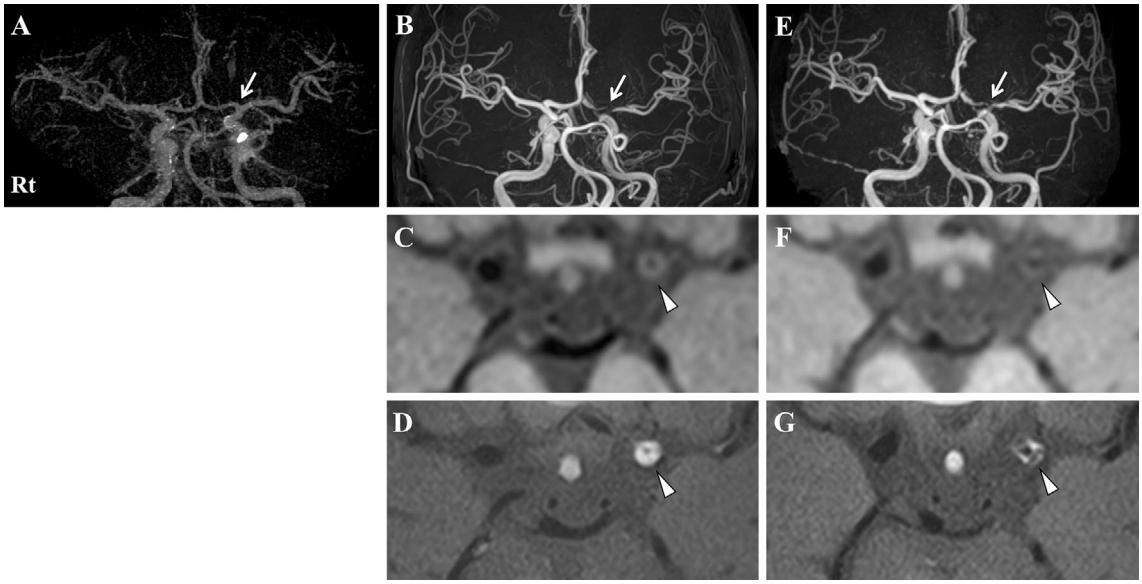

Figure 3. **Time course of vascular morphology in varicella zoster virus vasculopathy. (A) 3D reconstruction of contrast-enhanced CT 3 months before admission for follow-up of malignant lymphoma showed no stenosis or abnormal findings at the top of the left ICA. The reason for the blurred image is that the primary purpose was not for a vascular assessment. (B) MRA (time of flight, TOF; TR 18 ms, TE 3.9 ms) on 3-T MRI on admission. (C) T1-weighted imaging (TIWI; TR 650 ms, TE 16.5 ms) on 3-T MRI on admission showed the thickened vessel wall of the left internal carotid artery (ICA) compared with the contralateral ICA. (D) Gadolinium-enhanced 3D black-blood T1-weighted imaging (vessel wall imaging, VWI; TR 550 ms, TE 17 ms) on 3-T MRI on admission showed concentric enhancement in the thickened vessel wall of the left ICA. (E) MRA (TOF, TR 18 ms, TE 3.9 ms) on 3-T MRI seven months after admission showed improvement of the signal intensity of the blood flow at the top of the left ICA. (F) T1WI (TR 650 ms, TE 16.5 ms) on 3-T MRI seven months after admission showed improvement of vessel wall thickening of the left ICA. (G) VWI (TR 550 ms, TE 17 ms) on 3-T MRI seven months after admission showed decreased enhancement in the vessel wall of the left ICA. In addition, the left ICA vessel lumen was expanded. The white arrow indicates the top of the left ICA. The white arrowhead indicates the vessel wall of the left ICA.**

recurrence of stroke. She was discharged 31 days from admission and continued aspirin 200 mg per day.

MRA and VWI at 7 months after admission showed improvement of the stenosis of the left ICA and reduced vessel wall enhancement (Fig. 3E-G). The WEI of the stenotic lesion had decreased to 1.22. In addition, anti-VZV antibody IgM was negative, and the anti-VZV IgG antibody index (1.19) had also decreased by 7 months after admission. She showed no further exacerbations of neurological symptoms and no recurrent stroke, and she lived her daily life at home.

Discussion

We encountered a patient with acute stroke caused by progressive severe stenosis at the top of the left ICA after chemotherapy for follicular lymphoma who was diagnosed with VZV vasculopathy by intrathecal synthesis of anti-VZV antibody (1, 5).

To our knowledge, this is the first report of VZV vasculopathy after B-R. VZV reactivation occurs in 12.2% of non-Hodgkin lymphoma patients receiving chemotherapy (2). Most VZV reactivations occur within first two years after the diagnosis of lymphoma, and the risk factors are women, diabetes mellitus, and multiple courses of chemotherapy (2). The risk also depends on the kind of chemotherapy (2, 6). The present patient was treated with six courses of B-R before VZV reactivation. Lymphocytopenia continued after B-R, and this reduced cell-mediated immunity caused VZV reactivation, with vasculopathy consequently developing (Fig. 1). B-R is a standard treatment for several indolent B cell lymphomas (7). Bendamustine is known to cause myelosuppression, including lymphocytopenia, mostly with decreased CD4+ T lymphocytes and a decreased cell-mediated immunity over seven to nine months (8). Rituximab causes B cell depletion and induces substantial T cell depletion, mainly of CD4+ cells (9). Thus, B-R causes both T cell and B cell depletion (8) and leads to impaired cell-mediated immunity.

The morphological changes of the ICA before and after therapy for VZV vasculopathy were observed. A limited number of studies have reported the improvement of vascular morphology after treatment for VZV vasculopathy with long-term follow-up (10), and few reports have shown the time course of VZV vasculopathy from before the onset to

the recovery process. A previous study reported that VWI was useful for the follow-up of vascular morphology and evaluating the treatment effect of VZV vasculopathy (10). Furthermore, the present patient showed improvement of the WEI value (4) of stenotic lesions, which is thought to reflect the degree of vessel wall inflammation.

Although computed tomography angiography (CTA) three months before admission in the present patient showed no stenosis in the intracranial arteries, VWI on admission showed concentric severe stenosis with gadolinium enhancement, which is the characteristic finding of vasculitis at the top of the left ICA (11). Seven months after treatment, VWI showed improvement of the left ICA stenosis, a decreasing WEI, and vessel wall thickening. The patient showed deterioration and improvement of intracranial artery stenosis in association with VZV vasculopathy activity.

In the present patient, the stenosis limited to the top of ICA appeared to have been related to the pathological mechanism of VZV vasculopathy. Seventy percent of patients with VZV vasculopathy had vascular abnormalities on angiography, and 50% of them were distributed in both large and small arteries, 37% in small arteries exclusively, and 13% in large arteries exclusively (1). The trigeminal ganglia in which VZV is latently located predominantly project nerve fibers to the ipsilateral proximal middle cerebral artery (MCA), anterior cerebral artery (ACA), and the top of the ICA (12). VZV in the trigeminal ganglia reactivated without a simultaneous rash in the sacral ganglion distribution because 37% of VZV vasculopathy occurred without a rash (13), although the previous zoster infection in the current patient involved the left sacral distribution. Therefore, VZV reactivation in the trigeminal ganglia reaches the ICA wall transaxonally. After reaching the adventitia, the virus spreads transmurally, causing infection in the cerebral arteries (1). VZV-infected cells in the adventitia induce neutrophil, macrophage, and T lymphocyte chemotaxis (14), increase the levels of various soluble factors such as interleukin 6 (IL-6) and IL-8 (15), and cause disruption of the internal elastic lamina, intimal thickening, and decreased smooth muscle cells in the media (16).

In the current patient, the subclinical VZV reactivation in trigeminal ganglia caused vasculopathy five months after shingles without cranial nerve palsy. VZV reactivation can cause cranial nerve palsy, such as shingles of the trigeminal nerve and Hunt syndrome. However, our patient had vasculopathy and ischemic stroke without any cranial nerve palsies. This may be because of the different mechanisms between vasculopathy and cranial nerve palsy. Whereas vasculopathy is caused by reactivate VZV reaching transaxonally to blood vessels and inflammatory response, the major pathology of cranial nerve palsy after shingles and Hunt syndrome is viral neuritis (17, 18). Shingles is generally a monophasic disease, and the recurrence rate is less than 5% (19). Therefore, the present patient did not develop neuritis of the cranial nerve, as she had already presented shingles on the sacral distribution and been treated with amenamevir.

A previous review recommended treating VZV vasculopathy with intravenous acyclovir, 10-15 mg/kg three times daily, for a minimum of 14 days, and oral prednisone 1 mg/kg/day for five days (1). In the present patient, the dose and duration of acyclovir were sufficient, as intrathecal synthesis of anti-VZV antibody remained suppressed seven months after discharge. Increasing the dose of aspirin and methylprednisolone pulse therapy might have been effective to suppress the immune response and inflammatory cascade and improved the stenotic and gadolinium-enhanced vessel wall at the top of the ICA.

Conclusion

Progressive ICA stenosis due to VZV vasculopathy after chemotherapy for malignant lymphoma caused acute ischemic stroke. Treatment for VZV vasculopathy improved the intracranial stenotic lesion.

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

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