

## Brief Report

## TWO PATIENTS WITH UNUSUAL FORMS OF VARICELLA-ZOSTER VIRUS VASCULOPATHY

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**I**NFECTION of cerebral arteries by varicella-zoster virus (VZV) can produce unifocal or multifocal vasculopathy. Unifocal large-vessel vasculopathy (granulomatous arteritis) usually affects elderly immunocompetent persons, whereas multifocal vasculopathy occurs primarily in persons who are immunocompromised.<sup>1</sup> Unifocal large-vessel infarcts may follow zoster in a trigeminal distribution and are presumed to result from transaxonal transport of virus from trigeminal afferent fibers that innervate vessels of the anterior circulation.<sup>2</sup> Similarly, smaller infarcts in deep white and gray matter may reflect transport of VZV from trigeminal or cervical afferent fibers to smaller branches of vessels of the posterior circulation.<sup>2,3</sup> We encountered two patients with unusual forms of VZV vasculopathy. Detection of VZV antibody in cerebrospinal fluid and reduced ratios of the concentration of anti-VZV IgG in serum to that in cerebrospinal fluid, in conjunction with normally high ratios for total IgG and albumin, verified the viral cause of their vascular disease.

## CASE REPORTS

## Patient 1

In April 2001, zoster in a left sacral (S2) distribution developed in Patient 1, a 71-year-old man with chronic lymphocytic leukemia that was in remission. Despite treatment with oral valacyclovir (1000 mg three times daily for seven days), zoster spread to the right S2 dermatome. Lesions resolved in three to four weeks. In May 2001, bimodal headaches developed, along with mild confusion, foot numbness, and unsteady gait. Vibratory sensation was reduced in the toes, ankle jerks were absent, and gait was mildly

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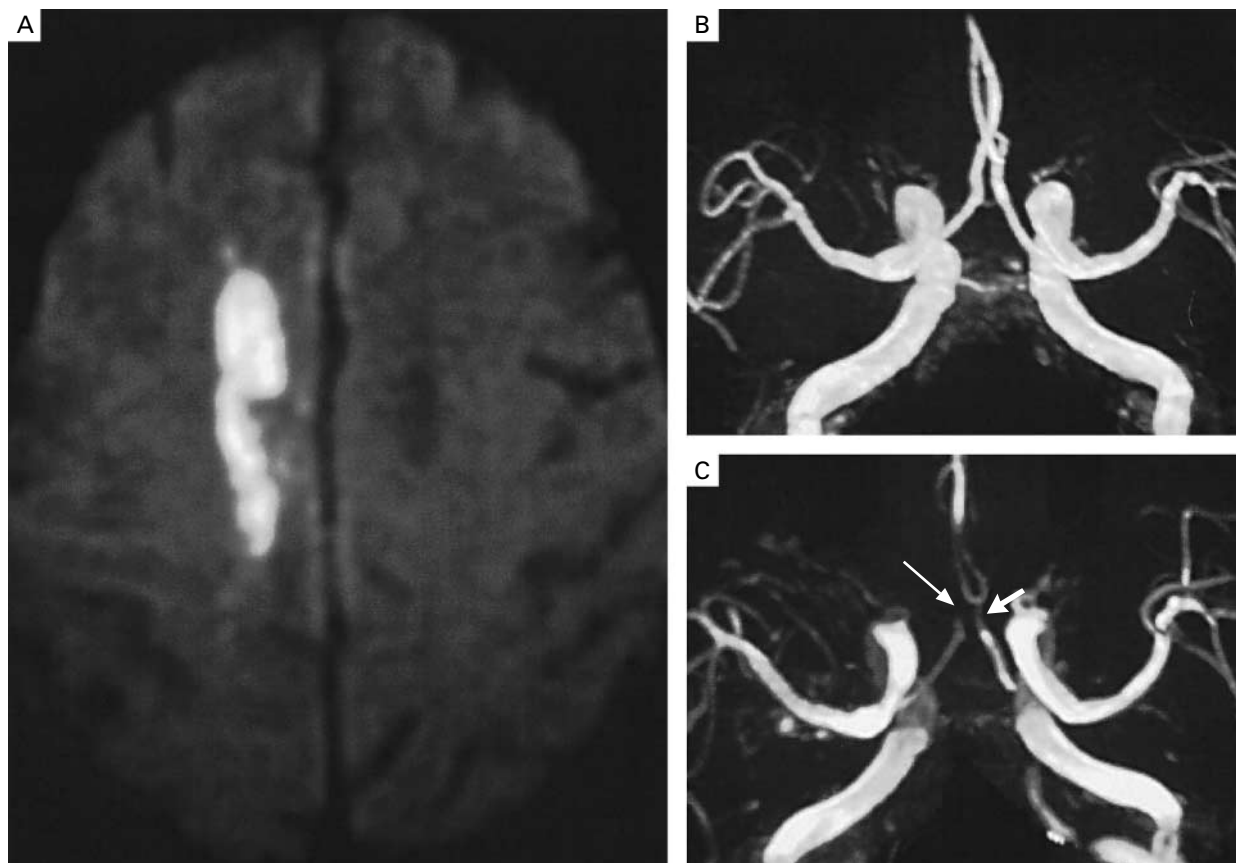
wide-based. The white-cell count was 12,100 per cubic millimeter, with a normal differential count. Magnetic resonance imaging (MRI) of the brain and magnetic resonance angiography were normal (Fig. 1B). Two cerebrospinal fluid examinations revealed extensive mononuclear pleocytosis, an elevated protein level, and a normal glucose level (Table 1). Polymerase-chain-reaction (PCR) analysis of the cerebrospinal fluid revealed no amplifiable VZV DNA.

Headaches, confusion, and imbalance resolved within two months. On October 15, 2001, the patient noted that he had difficulty finding words, numbness of the left hand, weakness of the left leg, and urinary urgency. Neurologic examination revealed halting speech, a flattened left nasolabial fold, mild weakness of the left side, an extensor plantar response on the left, and bilateral grasp reflexes. A complete blood count, electrolyte values, a blood-chemistry panel, and urinalysis were normal. MRI of the brain revealed an infarction in the right pericallosal distribution (Fig. 1A). Magnetic resonance angiography revealed occlusion of the anterior cerebral artery on the right side and stenosis on the left side (Fig. 1C). A third sample of cerebrospinal fluid (Table 1) was acellular, but the protein level, the total IgG level, and the rate of IgG synthesis were elevated, with three to four oligoclonal bands. PCR analysis revealed no amplifiable herpes simplex virus (HSV) or VZV DNA or antibody to HSV, but an enzyme-linked immunosorbent assay of cerebrospinal fluid<sup>4</sup> revealed an extraordinarily high titer (19.6) of anti-VZV IgG antibody. The ratio of the concentration of anti-VZV IgG antibody in serum to that in cerebrospinal fluid was 0.66:1, as compared with ratios of 77:1 for total IgG antibodies and 55:1 for albumin; these findings are consistent with intrathecal synthesis of anti-VZV IgG.<sup>5</sup> The patient received intravenous acyclovir (10 to 15 mg per kilogram three times daily for seven days), and the neurologic deficits improved within a week. A neurologic examination on December 3, 2001, was normal.

## Patient 2

In October 2000, zoster in a left ophthalmic distribution developed in Patient 2, an immunocompetent 76-year-old woman with a history of closed-angle glaucoma (base-line vision, 20/40 in the left eye and 20/100 in the right eye); she was treated with oral famciclovir (500 mg three times daily for 30 days). Pain resolved after two months, but itching persisted. In April 2001, dull pain developed over the left side of the forehead and scalp, extending to the vertex, and she reported a "film-like feeling" inside her left eyelid. The next day, she suddenly lost all vision in the left eye. Examination revealed only light perception in the left eye and 20/100 vision in the right eye. Intraocular pressures were normal. The left optic nerve was pale, without retinal pallor, edema, or cherry-red spot. Advanced arteriosclerotic changes were apparent in retinal vessels. A presumptive diagnosis of focal VZV vasculopathy was made, and the patient was treated immediately with intravenous acyclovir (10 mg per kilogram every eight hours). Within one to two days after treatment began, she reported seeing "blotches that moved," and within 48 hours, she could identify faces. Intravenous acyclovir was continued for a total of 10 days, at which time she regained her base-line level of vision.

Before treatment, the serum contained IgM antibody to VZV. In addition, the cerebrospinal fluid did not contain amplifiable HSV or VZV DNA or anti-HSV antibody, but there was IgG antibody to VZV in cerebrospinal fluid. The ratio of the concentration of anti-VZV IgG in serum to that in cerebrospinal fluid was 131:1, whereas the ratio for total IgG was 317:1 and the ratio for albumin was 182:1, which is consistent with intrathecal synthesis of anti-VZV IgG.<sup>5</sup> After treatment, the sedimentation rate and the results of computed tomography (CT) and MRI of the brain, Doppler ultrasonography of the carotid arteries, magnetic resonance angiography of extracranial and intracranial vessels, transesophageal echocardiography, and examination of the cerebrospinal fluid were all normal. One month later, the "film-like feeling" inside the patient's left eyelid recurred, and she was treated again with intravenous acyclovir



**Figure 1.** Varicella–Zoster Virus Vasculopathy and Infarction in Patient 1.

In Panel A, a diffusion-weighted image shows restricted diffusion in the territory of the right anterior cerebral artery, indicating the presence of acute infarction. Three-dimensional time-of-flight magnetic resonance angiography of the circle of Willis shows normal anterior cerebral arteries five months before infarction (Panel B) and marked narrowing of anterior cerebral arteries at the time of infarction (Panel C); a new gap disrupts the flow at the junction of the A1 and A2 segments of the right anterior cerebral artery, indicating the presence of occlusion on the right side (long arrow) and marked stenosis on the left side (short arrow).

(10 mg per kilogram every eight hours) for an additional 10 days. She has been asymptomatic since that time.

### DISCUSSION

After reactivation from ganglia, VZV may migrate transaxonally to infect cerebral arteries, resulting in unifocal or multifocal vasculopathy. Analysis of clinical features, MRI, magnetic resonance angiography, PCR analysis, and measurement of antiviral antibody in serum and cerebrospinal fluid were used to study two patients in whom transient ischemic attacks developed months after the occurrence of zoster infection. In the first patient, zoster developed in a sacral distribution, followed by vasculopathy in a branch of the anterior cerebral artery; in the second patient, zoster in a trigeminal distribution developed, followed by ipsilateral, posterior ischemic optic neuropathy. In each case, there was a reduced ratio of the concentration of anti-

VZV IgG in serum to that in cerebrospinal fluid in conjunction with normally high ratios for total IgG and albumin. Both cases were diagnosed quickly, and the patients were treated with intravenous acyclovir and had complete resolution of neurologic and visual deficits.

Most unifocal strokes after reactivation of VZV occur in elderly immunocompetent persons with recent zoster in a contralateral trigeminal or cervical distribution. Infarcts usually occur in the distribution of the carotid, anterior, or middle cerebral arteries, although single deep-seated infarcts in the thalamus,<sup>6</sup> brain stem,<sup>7,8</sup> and spinal cord<sup>9</sup> also occur. In immunocompromised patients, VZV-related infarcts are usually bilateral.<sup>10,11</sup>

In Patient 1, zoster developed in a bilateral sacral distribution, followed by ischemia of the anterior cerebral artery. Although focal deficit was restricted to the left

**TABLE 1.** FINDINGS IN CEREBROSPINAL FLUID FROM PATIENT 1, WHO HAD UNIFOCAL VARICELLA-ZOSTER VIRUS VASCULOPATHY OF THE PERICALLOSAL ARTERY.

DATE OF LUMBAR PUNCTURE	WHITE CELLS	RED CELLS	DIFFERENTIAL COUNT	GLUCOSE LEVEL	TOTAL PROTEIN LEVEL
	no. of cells/mm <sup>3</sup>		% mononuclear	mg/dl	
6/1/01	260	120	98	78	230
6/13/01	320	14	100	75	267
10/18/01	0	0	—	78	153

side, angiography revealed disease in both anterior cerebral arteries, as might be expected in an immunocompromised patient. VZV DNA was not present in cerebrospinal fluid, but the anti-VZV IgG antibody titer was extraordinarily high and the ratio of the concentration of anti-VZV IgG in serum to the concentration in cerebrospinal fluid was reduced as compared with the ratios of total IgG and albumin. Diagnosis of VZV-induced vasculopathy, followed immediately by treatment with intravenous acyclovir, led to complete resolution of all neurologic deficits. The anatomical distance between sacral zoster and remote vasculopathy of the anterior cerebral artery is even greater than that described in a fatal case of multifocal VZV disease of the central nervous system after zoster in a thoracic distribution.<sup>10</sup> Although it is unclear how VZV vasculopathy develops in dermatomes distant from the original site of zoster, it is possible that the reactivation of VZV from sacral ganglia occurred simultaneously with reactivation without rash from both trigeminal ganglia and that virus then spread along trigeminal afferent fibers to the anterior cerebral arteries. VZV has been shown to produce severe cerebral vasculopathy<sup>12</sup> and encephalomyeloradiculitis<sup>13</sup> without rash.

In Patient 2, zoster in a left ophthalmic distribution developed, followed, months later, by sudden loss of vision in the left eye. The presence of acute visual loss and a pale optic nerve without retinal edema, pallor, or cherry-red spot indicated involvement of the posterior ciliary artery. The pale optic nerve probably reflected long-standing VZV vasculopathy of the posterior ciliary artery. As in Patient 1, there was a reduced ratio of the concentration of anti-VZV IgG in serum to that in cerebrospinal fluid. In addition, the serum contained IgM antibody to VZV, indicative of active infection. Prompt antiviral treatment resulted in complete resolution of neurologic deficit. The interval between zoster and visual loss was five months, which is consistent with reports of VZV vasculopathy occurring up to six months after zoster in a trigeminal

distribution.<sup>14</sup> Visual loss due to occlusion of the central retinal artery two weeks after zoster in a trigeminal distribution has also been described.<sup>15</sup>

Detection of intrathecal antibody to VZV during vasculopathy suggests that stroke is related to VZV. Humans produce more than three times their total volume of cerebrospinal fluid daily, a turnover rate that would render antiviral antibody undetectable in cerebrospinal fluid within days after zoster unless infection was protracted. In patients with chronic VZV vasculopathy, productive viral infection in cerebral arteries has been demonstrated.<sup>12</sup> If it were known that intrathecal antibody production does not occur months after uncomplicated zoster, the presence of intrathecal antibody to VZV during vasculopathy would be even more compelling. However, because patients with uncomplicated zoster do not undergo repeated cerebrospinal fluid examination, the usual amount of intrathecal antibody production, if any, months later, is unknown. Nevertheless, in a longitudinal study of 50 patients with zoster, 5 patients underwent cerebrospinal fluid examination for anti-VZV IgG once during the first month after the occurrence of zoster infection and two or three additional times between 31 and 105 days later.<sup>16</sup> In two of the five patients, the anti-VZV antibody titer remained the same; unfortunately, no further clinical information was provided. In the other three patients, anti-VZV IgG disappeared after one month. Intrathecal antibody production was not studied in any of the five patients.

The fact that intrathecal production of anti-VZV antibody has been associated with vasculopathy on multiple occasions,<sup>17,18</sup> combined with the documented loss of anti-VZV antibody in cerebrospinal fluid after one month in some patients with uncomplicated zoster,<sup>16</sup> provides strong evidence that intrathecal production of antibody to VZV indicates active viral infection. In fact, in our first patient, the ratio of the concentration of anti-VZV IgG in serum to that in cerebrospinal fluid was less than 1:1, demonstrating that more anti-VZV antibody was being generated intrathecally than systemically.

Both patients had transient ischemic attacks, though these were different from the transient ischemic attacks that have been described in other patients with VZV vasculopathy,<sup>14</sup> and the stuttering course of central nervous system disease was emphasized in a prototypical case of VZV vasculopathy without rash.<sup>12</sup> Clinicians caring for patients who have transient ischemic attacks after zoster must be alert to the probability that impending stroke in elderly patients is related to VZV and is treatable.

Our report expands the list of known manifestations of protean VZV vasculopathy. The reports document the development of recurrent vasculopathy presenting with transient ischemic attacks, including posterior is-

chemic optic neuropathy, remote from the site of acute zoster infection and months after the infection occurs. Detection of antibody to VZV in cerebrospinal fluid, even without amplifiable VZV DNA, can be diagnostic. Recognition of the wide spectrum of VZV vasculopathy and its proclivity to recur even at a distance from the site of a preceding zoster infection is essential, since effective antiviral therapy can be curative. Finally, oral antiviral treatment is insufficient for treating VZV vasculopathy; intravenous acyclovir is required, and treatment may need to be repeated if ischemia recurs.

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