Multifocal Varicella-Zoster Virus Vasculopathy Without Rash

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A 51-year-old woman with CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) developed stepwise progressive focal neurological deficits without zoster rash. Multifocal ischemic infarcts were seen on magnetic resonance imaging, and cerebral angiography revealed focal stenosis of arteries affecting the intracranial circulation. A brain biopsy was nondiagnostic. Virological etiology of the disease was verified by the detection of varicella-zoster virus antibody in cerebrospinal fluid and by reduced serum–cerebrospinal fluid varicella-zoster virus IgG ratios (compared with normally high ratios of total IgG and albumin). Treatment with intravenous acyclovir stabilized but did not significantly improve her neurological deficits.

The main central nervous system complication of varicella-zoster virus (VZV) reactivation is vasculopathy. Both unifocal and multifocal vasculopathy usually develops days to weeks after zoster rash. Multifocal VZV vasculopathy may also occur without rash, thus making diagnosis difficult. Herein, we describe a patient with multifocal central nervous system vasculopathy without rash that was confirmed virologically to be caused by VZV. This report illustrates the need for early antiviral treatment, and emphasizes the diagnostic value of VZV antibody detection in the serum and cerebrospinal fluid (CSF).

REPORT OF A CASE

In July 2002, a 51-year-old woman with CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) developed right peripheral facial weakness without auricular or pharyngeal rash. Initially diagnosed as having scleroderma in 1985, she had been treated years earlier with oral prednisone (unknown dosage and duration). Five days after her current presentation, brain magnetic resonance imaging (MRI) revealed an enhancing lesion of the right facial nerve. She was given oral acyclovir (800 mg 5 times daily) and prednisone (60 mg/d for 2 weeks, tapered to 10 mg/d over 4 weeks). Two weeks later, she complained of brief periods of malaise, confusion, and disorientation. In August 2002, she noted intermittent vertigo, confusion, decreased hearing on the right, right-sided clumsiness, and left leg weakness. Neurological examination revealed right peripheral facial weakness, left hemiparesis, and ataxia. Brain MRI again showed an enhancing lesion of the right facial nerve and new deep-seated enhancing lesions in the brainstem, thalamus, caudate nucleus, internal capsule, and left temporal lobe. Treatment with oral prednisone (10 mg/d) was continued. Oral acyclovir therapy was stopped after 21 days.

By September 2002, the patient could not walk. There was no rash. Neurological examination revealed intermittent confusion, nystagmus, a left third nerve palsy, facial diplegia (worse on the right), a spastic quadriparesis (greater on the left), brisk deep tendon reflexes on the left, ankle clonus, and extensor plantar responses. A third brain MRI examination showed mul-
Multiple areas of acute and subacute infarction in the same areas previously described, with new enhancing foci in the frontal, parietal, and occipital lobes and in the hippocampus, insula, and periventricular white matter (Figure 1). Transthoracic and transesophageal echocardiograms were normal. Brain magnetic resonance angiography revealed patent intracranial vasculature without focal stenosis. A 3-vessel cerebral angiogram showed irregularity in the left M2 branches and in the distal branches of the right posterior cerebral artery consistent with vasculopathy (Figure 2).

In late September 2002, the patient had a generalized tonic-clonic seizure; electroencephalography revealed partial status epilepticus in the left parieto-occipital region. She was treated with an 800-mg loading dose of fosphenytoin sodium, followed by 300 to 400 mg/d, initially given intravenously and then converted to oral dosing. Serum protein S was 47% (normal, 59%-131%), and antithrombin III was 67% (normal, 80%-120%). The serum did not contain lupus anticoagulant or anticardiolipin antibodies. Antinuclear antibody was 16.7 (normal, <1.5). Antibodies to extractable nuclear antigens (Smith, ribonucleoprotein, histidine-tRNA synthetase [Jo-1], Sjögren syndrome antigens A and B, topoisomerase I [Scl-70], centromere, and histone) were negative; antiribosomal ribonucleoprotein was positive. This antinuclear antibody pattern is consistent with a nonspecific connective tissue disease. The CSF opening pressure was 24 cm H₂O; CSF protein and glucose levels were normal. There were 904 red blood cells and 4 white blood cells per cubic millimeter and 4 to 5 oligoclonal bands in the CSF; cultures for bacteria, acid-fast bacilli, and fungi were negative. There was no amplifiable herpes simplex virus (HSV) 1, HSV-2, or VZV DNA in the CSF. A brain biopsy revealed no pathological changes.

The serum contained IgM antibody to VZV but not to HSV. The CSF contained IgG antibody to VZV but not to HSV (Table). The ratio of the concentration of anti-VZV IgG in serum to that in CSF was 4.7, whereas the ratio for total IgG was 93 and for albumin was 88, consistent with intrathecal synthesis of anti-VZV IgG.¹

A diagnosis of multifocal VZV vasculopathy was made, and the patient was treated with intravenous acyclovir, 10 mg/kg of body weight every 8 hours for 22 days, and with intravenous methylprednisolone, 1 g/d for 5 days.

![Figure 1](image1.png)

**Figure 1.** A, Axial diffusion-weighted image. Restricted diffusion in the midbrain and mesial temporal lobes indicates areas of acute infarction. B, Axial fluid-attenuated inversion recovery sequences. Increased signal intensity in the bilateral thalami, left caudate, left corona radiata, and occipital, parietal, and frontal lobes demonstrates multifocal acute and subacute infarcts involving the anterior and posterior circulation.

![Figure 2](image2.png)

**Figure 2.** Cerebral angiogram shows focal areas of stenosis (white arrows) and poststenotic dilatation (black arrows) involving the right posterior cerebral artery.
followed by 1 mg/kg of body weight daily for 31 days. No new clinical deficit or lesions on MRI developed; however, the severity of her condition (decreased arousal, spastic quadriaparesis, severe dysphagia, and tracheostomy dependence) necessitated transfer to a nursing home.

We report a case of VZV multifocal vasculopathy that developed in the absence of zoster rash. Usually, VZV multifocal vasculopathy develops in immunocompromised individuals with a recent history of zoster. However, VZV multifocal vasculopathy also occurs without rash. One fatal case was in an immunocompetent individual in whom productive virus infection was found at autopsy in cerebral arteries. In another case, an HIV-infected individual was diagnosed early on, based on detection of VZV DNA and antibody in CSF, and was successfully treated with immediate intravenous acyclovir. The development of VZV multifocal vasculopathy without zoster rash is not surprising because aseptic meningitis, myelitis, peripheral and cranial neuropathies, and a fatal case of meningoradiculitis, all virologically verified as VZV-induced, have also been described without zoster rash.

Cerebrospinal fluid analysis for VZV DNA and antibody is essential in the diagnosis of VZV vasculopathy. Even if VZV DNA is not present, the presence of antibody to VZV together with reduced ratios of serum-CSF VZV IgG (compared with normally high serum–CSF ratios of albumin or total IgG) can verify the diagnosis. The diagnosis of VZV vasculopathy is unlikely to be made by brain biopsy because viral DNA and antigen are restricted to brain arteries, a factor that delayed determination of the cause of vasculopathy in our patient. Overall, even in the absence of amplifiable VZV DNA in the CSF, antibody studies for VZV IgM and IgG are critical. Varicella-zoster virus antibody detection is especially important in immunocompetent or immunocompromised individuals with multifocal neurological deficits, including those patients with radiological indication of multifocal infarction or angiographic evidence of stenosis.

The role of our patient’s rheumatologic disorder in the development of VZV vasculopathy is unclear. Immunological abnormalities in patients with CREST syndrome include hypergammaglobulinemia, as well as a scleroderma-like lesion similar to that seen in graft-vs-host disease. Although a patient with scleroderma and VZV encephalitis has been described, there are no data indicating that patients with scleroderma or CREST syndrome are at increased risk of developing VZV vasculopathy. In fact, the most likely cause of VZV reactivation in our patient was probably treatment with corticosteroids.

Initial treatment of our patient with oral acyclovir was ineffective. Earlier recognition of a pattern of stepwise progressive focal neurological deficits without zoster rash would have signaled the need for immediate administration of intravenous acyclovir. By the time the patient reached our institution (approximately 7 weeks after initial presentation), her neurological deficits were severe and extensive. Treatment with intravenous acyclovir stopped further progression but did not significantly improve her neurological deficits. Patients with suspected VZV vasculopathy, with or without zoster rash, should be treated empirically with intravenous acyclovir (10-15 mg/kg of body weight 3 times daily for 7-10 days) while VZV antibody testing is under way.

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