Varicella-Zoster Virus and Cerebral Aneurysm: Case Report and Review of the Literature

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We report a case of varicella-zoster vasculopathy that occurred in a 42-year-old renal transplant recipient with concurrent vertebral artery aneurysm and dissection. The patient was successfully treated with embolization and acyclovir therapy. Here, we review the English literature regarding the association of varicella-zoster virus infection with cerebral aneurysm.

Varicella-zoster virus (VZV) causes a variety of neurological complications. It can uncommonly infect the blood vessels of the brain, producing vasculitis resulting in thrombosis, hemorrhage, and stroke [1,2]. Only 8 cases of cerebral aneurysm or dissection in association with VZV infection have been reported in the English literature, and a causal relationship has yet to be confirmed.

Case report. A 42-year-old man presented to our emergency department with a 2-week history of weakness, chills without fever, headache, neck pain, and nonproductive cough. He had received a cadaveric kidney transplantation 22 years earlier, after having poststreptococcal glomerulonephritis. The patient experienced chronic rejection of his graft. He received a living, related kidney transplantation 10 months before presentation to the emergency department, without any complications. The patient was receiving prednisone (7.5 mg daily), mycophenolate mofetil (1000 mg every 12 h), and tacrolimus (2 mg every 12 h). Serum cytomegalovirus antibody titers were equivocal before the most recent transplantation. The patient reported having chickenpox in the past, and his serum VZV IgG antibody titer was positive (4.20 index value; a VZV IgG reported having chickenpox in the past, and his serum VZV equivocal before the most recent transplantation. The patient was successfully treated with embolization and acyclovir therapy. Here, we review the English literature regarding the association of varicella-zoster virus infection with cerebral aneurysm.

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Case report. A 42-year-old man presented to our emergency department with a 2-week history of weakness, chills without fever, headache, neck pain, and nonproductive cough. He had received a cadaveric kidney transplantation 22 years earlier, after having poststreptococcal glomerulonephritis. The patient experienced chronic rejection of his graft. He received a living, related kidney transplantation 10 months before presentation to the emergency department, without any complications. The patient was receiving prednisone (7.5 mg daily), mycophenolate mofetil (1000 mg every 12 h), and tacrolimus (2 mg every 12 h). Serum cytomegalovirus antibody titers were equivocal before the most recent transplantation. The patient reported having chickenpox in the past, and his serum VZV IgG antibody titer was positive (4.20 index value; a VZV IgG titer >1.10 index value was considered to be positive). On examination, the patient was afebrile, lethargic, confused, and without skin lesions. CT images of his head were normal, and a lumbar puncture revealed xanthochromic CSF. He had a WBC count of 208 cells/μL (with 4% polymorphonuclear leukocytes), an RBC count of 500 cells/μL, normal glucose concentration, and a protein concentration of 256 mg/dL. Results of Gram stain and culture were negative. Because the patient was immunocompromised, a CSF sample was obtained for PCR for herpes simplex virus, Epstein Barr virus, and VZV. A cerebral angiogram revealed a 3 × 4.5-mm dissecting aneurysm of the right intracranial vertebral artery at the origin of the inferior cerebellar artery (figure 1), and a successful stent-assisted coil embolization of the aneurysm was performed. PCR of a CSF sample for VZV subsequently revealed a markedly high VZV load (2.6 × 10² copies/mL). Intravenous acyclovir therapy (10 mg/kg [750 mg] every 8 h) was started, and the doses of immunosuppressive medications were reduced. MRI of the brain revealed multiple T2 signal abnormalities throughout the white matter (figure 2). The patient’s confusion gradually resolved, and although his speech remained slow, he was otherwise neurologically intact. His course was complicated by cytomeglovirus viremia, which was successfully treated with gancyclovir. A second lumbar puncture was performed 2 weeks after the initial lumbar puncture. Examination of the new CSF sample revealed a WBC count of 21 cells/μL, an RBC count of 8 cells/μL, a protein concentration of 175 mg/dL, and a VZV load of 400 copies/mL. Results of PCR for cytomegalovirus were negative. Two months later, the patient complained of “black spots” in his visual field. Ophthalmologic examination revealed bilateral acute retinal necrosis. The patient was treated with bilateral intravitreal injections of gancyclovir and foscarnet. PCR for VZV of a sample obtained through intravitreal tap revealed a VZV load of 3.4 × 10⁴ copies/mL.

Discussion. VZV can cause various neurological syndromes as part of primary or reactivated disease; such syndromes include postherpetic neuralgia, myelitis, and encephalitis. Although VZV can infect a variety of neural cells (e.g., neurons, glial cells, and ependymal cells), the detection of VZV DNA in blood vessels of the brain has led to the realization that the CNS manifestations of encephalopathy are predominantly the result of arterial disease [1, 3]. The virus may infect cerebral arteries by migrating along neurons or through hematogenous spread [4, 5]. Furthermore, VZV encephalitis may be either unifocal, affecting the large cerebral arteries, or multifocal, affecting the smaller arteries, and often occurs in immunocompromised individuals in the absence of rash [2].
Although vasculitis secondary to VZV infection has been well described in the literature, aneurysms and dissection related to VZV infection have been reported only sporadically. A search of the Medline database for English language literature with use of the search terms “varicella-zoster,” “herpes zoster,” “aneurysm,” and “dissection” yielded only 6 relevant articles [5–10]. A review of secondary references did not identify any additional cases.

The first report linking VZV infection to CNS aneurysm was from 1980. Gursoy et al. [6] reported a case in a healthy 24-year-old woman who initially experienced zoster ophthalmicus, peripheral facial palsy, and contralateral hemiplegia. Findings of examination of a CSF sample were normal, as were those of the initial angiogram for detection of aneurysm. After 1 month, the patient developed new neurologic symptoms, with unilateral hypoacusia and a left Horner syndrome, and a second angiogram revealed an aneurysm in the left intrapetrosal internal carotid artery. The aneurysm was treated with ligation of the artery.

The first case of CNS aneurysm rupture attributed to VZV was recorded by Fukumoto et al. [7] in 1986. A 70-year-old man died after cardiac arrest and subarachnoid hemorrhage. Before his death, the patient noted that he had had painful skin lesions (not further described) in the occipital region ∼2 months earlier. His serum VZV antibody titer was positive. On autopsy, granulomatous angiitis was noted in a single fusiform basilar artery aneurysm. Immunohistochemical staining was positive for VZV in the wall of the aneurysm.

O’Donohue and Enzmann [8] reported 2 additional cases of CNS angiitis associated with aneurysm. A 67-year-old man presented with left hemiparesis after having herpes ophthalmicus of the right eye 3 weeks earlier. An angiogram revealed a 3-mm aneurysm in the right anterior choroidal artery. In addition, a 33-year-old woman who had received a diagnosis of herpes ophthalmicus 4 months earlier presented with mental status changes after a headache. No focal neurological deficits were noted, and an arteriograph revealed a 5-mm aneurysm of the left anterior cerebral artery.

In 1998, Fulmer et al. [9] described a 6-year-old HIV-positive girl who presented with a 3-day history of cough, vomiting, and fever, followed by headache and seizure. CT revealed a subarachnoid hemorrhage. An arteriogram demonstrated a basilar tip aneurysm. Also noted were fusiform aneurysms of the internal carotid, middle cerebral, and anterior cerebral arteries. On autopsy, immunohistochemical staining was positive for VZV in dilated vessels and smaller vessels of the brain parenchyma.

Finally, Saraya et al. [5] described a 36-year-old HIV-positive man who was admitted to the hospital with zoster ophthalmicus, encephalomeningitis, and a concurrent vesicular rash on his knee. A diagnosis of VZV infection was made after results of PCR for VZV DNA were positive and the IgG level in CSF was determined to be positive. His condition was complicated by right leg paralysis. A magnetic resonance angiograph revealed multiple, small-vessel, cerebral aneurysms with a stenotic lesion in the middle cerebral artery and infarction in the middle cerebral artery distribution.

Similar to the paucity of literature regarding VZV infection–related aneurysms, only 2 patients have been reported to have had arterial dissection associated with VZV infection; the cases
involved the cervical arteries in both patients [10]. A 15-year-old boy presented with zoster ophthalmicus and developed contralateral hemiparesis while jogging 4 weeks later. A cerebral angiogram revealed a cervical artery dissection. A 4-year-old boy developed hemiplegia while wrestling with another child. He had had chickenpox 2 weeks earlier. A cerebral angiogram revealed an internal cervical artery dissection. Both patients recovered both clinically and radiographically. The diagnoses of VZV encephalopathy in these cases were clinical.

Dissections of the vertebral artery most commonly arise from trauma; however, infections have been thought to play a role in both cervical and vertebral dissections [11, 12]. Some authors have attributed the association of infection with dissection to minor unrelated trauma (e.g., vigorous exercise) [13] or trauma that occurs as the result of infection (e.g., coughing, sneezing, and vomiting) [14]. However, although minor trauma and strenuous exercise are frequent events, arterial dissections occur rarely in these contexts [10, 11]. It is possible that infection of the wall of an artery in the CNS may increase the propensity of the artery to dissect if it is subjected to further trauma, or alternatively, there may be underlying non–infection-related arterial abnormalities, such as fibromuscular dysplasia [14], which confer an increased risk of dissection during subsequent infection.

In the case that we report above, there was no history of trauma reported by the patient, even with careful questioning.

In addition to our knowledge, there have been no reports of VZV infection–related dissections or aneurysms of the vertebral artery, as occurred in our case.

We believe that our patient had VZV-associated vascular disease of the right vertebral artery that led to a weakened vessel wall, aneurysm formation, and subsequent dissection as a result of inflammation caused by the infection. Our hypothesis is strengthened by the fact PCR of the patient’s CSF sample revealed a VZV load of $2.6 \times 10^7$ copies/mL, making the diagnosis of VZV encephalopathy very likely [3]. It is also possible that the aneurysm could have been hereditary in nature and may have been present prior to the development of the encephalopathy. In this scenario, perhaps VZV infection might have led to further weakening of the vessel with dissection.

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**References**