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Case report

Varicella-zoster virus (VZV) multifocal vasculopathy in a patient with systemic lupus erythematosus — a diagnostic and treatment dilemma

Stephen Osiro*, Nadim Salomon

Division of Infectious Diseases, Department of Medicine, Mount Sinai Beth Israel, New York, NY, United States

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ABSTRACT

Cerebral vasculopathy due to varicella-zoster virus (VZV) infection is well-documented. We report a fatal case of VZV multifocal vasculopathy in a patient with systemic lupus erythematosus (SLE) who presented with subacute changes in mental status and had multiple areas of hemorrhagic infarcts on brain imaging. However, the correct diagnosis was delayed by several confounding factors including the absence of zoster rash, normal cerebral angiography, persistently low cerebrospinal fluid (CSF) glucose and negative initial polymerase chain reaction (PCR) for VZV DNA in the CSF. Our case and literature review suggests that the sensitivity of PCR for VZV DNA in the CSF is low in VZV vasculopathy and clinical suspicion of this disease in the setting of characteristic imaging findings could be crucial to timely diagnosis.

Introduction

Varicella zoster virus (VZV) is a neurotropic alphaherpesvirus. It causes primary infection in humans and then becomes latent in the autonomic, dorsal root and cranial nerve ganglia [1]. A decline in the virus-specific cell-mediated immunity can lead to its reactivation from the ganglia and transaxonal migration to the arteries where it causes infection. The latter is followed by pathological vascular remodeling and either ischemic or hemorrhagic stroke when cerebral arteries are involved [1,2].

Multifocal vasculopathy is a rare form of VZV vasculopathy which affects small and medium-sized cerebral vessels. The disease is mostly seen in immunocompromised patients such as those with acquired-immunodeficiency syndrome (AIDS) or organ transplant recipients [1].

We report a fatal case of multifocal VZV vasculopathy in a patient with lupus nephritis who presented with subacute mental status changes but whose diagnosis was delayed by several confounding factors.

Case

A 21 year old female presented to our hospital with increasing lethargy, weakness and worsening mental status for 4 days. Her medical history included lupus nephritis and auto-immune hemolytic anemia. She was taking prednisone 30 mg daily, mycophenolate mofetil 1500 mg twice a day and hydroxychloroquine 200 mg twice a day. The patient had immigrated to the United States from China 7 months prior and was living with her family in New York City. She had no contacts with pets and denied any recent travel.

On physical exam, she appeared weak and frail, responding only to a few commands. She had a low-grade fever of 100.0 °F and tachycardia (heart rate of 144 beats/min). Her neck was supple with no signs of meningismus. Labs showed a leukocyte count of 5.0 K/μL, hemoglobin of 11.1 g/dL, platelet count of 136 K/μL, creatinine of 0.9 mg/dL, and lactate dehydrogenase of 1932 U/L. Coagulation profile, C-reactive protein (1.1 mg/dL), erythrocyte sedimentation rate (12 mm/h), and the complements C3 (90 mg/dL) and C4 (32 mg/dL) were normal. Liver function test showed an albumin of 2.1 g/dL, but was otherwise normal.

Chest X-ray did not show any infiltrates. Magnetic resonance imaging (MRI) of the brain revealed confluent areas of abnormal signal involving the bilateral frontal and temporal lobes as well as diffuse leptomeningeal enhancement (Fig. 1). Brain magnetic resonance angiogram (MRA) was normal. Cerebrospinal fluid (CSF) analysis showed a glucose of 26 mg/dL, protein of 511 mg/dL, leucocyte (WBC) count of 39 cells/μL (68% lymphocytes, 1% neutrophils), and red blood cell count (RBC) of 2970 cells/μL. The CSF culture was negative as was polymerase chain reaction (PCR) tests for herpes simplex virus (HSV), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV). The patient was started empirically on intravenous broad-spectrum antibiotics, acyclovir 10 mg/kg every 8 h and anti-tuberculous therapy consisting of isoniazid plus pyridoxine, ethambutol, pyrazinamide and rifampin.

Her mental status did not improve, so after 3 days lumbar puncture was repeated. Elevated opening pressure of 49 cm H_2O was recorded,

* Corresponding author.
E-mail address: berilonson@gmail.com (S. Osiro).

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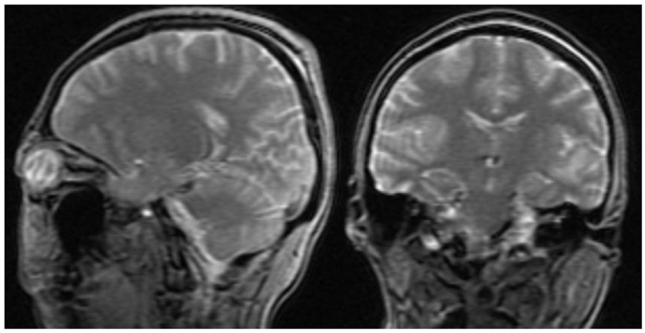

Fig. 1. Magnetic Resonance Imaging (MRI) of the brain showing confluent areas of abnormal signal involving the bilateral frontal and temporal lobes as well as diffuse leptomeningeal enhancement.

but the CSF protein (207 mg/dL) and glucose (24 mg/dL) were largely unchanged. CSF PCR for herpesviruses including VZV again returned negative. The antibiotics were discontinued due to negative cultures. However, both the acyclovir and anti-tuberculous therapy were continued. A week later, the patient became more lethargic and developed new right cranial nerve VI palsy. Computed tomography (CT) of the head showed lucency with mass effect in the bilateral cerebral hemispheres (Fig. 2) which had progressed compared to the initial brain MRI. A third lumbar puncture was done and showed opening pressure of 43 cm H_2O. CSF study revealed WBC count of 50 cells/μL (91% lymphocytes), RBC count of 1890 cells/μL, glucose of 24 mg/dL and protein of 363 mg/dL. VZV DNA was detected by PCR on this CSF sample. The patient was diagnosed with VZV vasculopathy and acyclovir dose was increased to 15 mg/kg every 8 h while anti-tuberculous therapy was discontinued. Unfortunately, she died two weeks after admission. Final CT scan of the brain before she expired showed extensive hemorrhage and white matter edema (Fig. 3).

Discussion

Varicella zoster virus is known to infect the cerebral arteries leading to vasculopathy with protean manifestations [3,4]. These different patterns have significant overlap in the same patient which may serve as a useful clue to the diagnosis [1]. Depending on the cerebral arteries involved, VZV infection can cause disease which is either unifocal or multifocal. Large vessel vasculopathy, which typically affects immunocompetent individuals, often presents as acute focal deficit weeks to months after an episode of trigeminal herpes zoster; an occurrence that has been referred to as herpes zoster ophthalmicus with delayed contralateral hemiplegia [1,5].

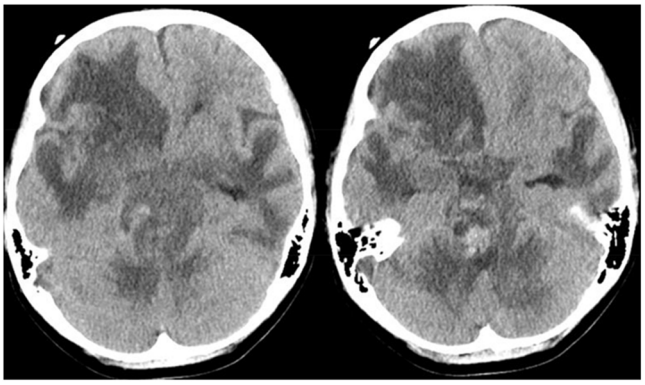

Fig. 3. CT scan of the brain showing interval expansion of the intraparenchymal hemorrhage within the pons, with compression of the fourth ventricle. Multiple areas of brain edema in the right and left cerebral hemispheres, cerebellar hemispheres, thalami, as well as the midbrain and pons are also shown.

Small-vessel or multifocal vasculopathy, on the other hand, affects intraparenchymal arterioles leading to small vessel ischemia, demyelinating lesions or hemorrhage. It is a disease immunocompromised patients, such as organ transplant recipients, or patients with AIDS [1,5]. Up to 40% of patients do not have a preceding herpes zoster rash. Patients present with subacute and non-specific symptoms which may include headaches, altered mental status, vomiting, or seizures [1].

Supportive evidence to assist with the diagnosis of VZV vasculopathy includes CSF studies and neuroimaging. MRI is abnormal in 97% of unifocal vasculopathy and typically shows ischemic or hemorrhagic lesions, especially at the gray-white matter junctions. Angiography reveals focal narrowing or occlusion of involved vessels and is abnormal in 70% of patients [1,5]. Lymphocytic pleocytosis (seen in 67% of cases) and elevated protein (discussed below) are characteristic findings on CSF, but are non-specific. Although PCR for VZV DNA in the CSF is a useful confirmatory test with a high specificity, greater than 95%, it only has 30% sensitivity which limits its reliability [1,5]. According to Aberle et al. [6], severity of VZV CNS disease may correlate with CSF viral load, with significantly higher viral loads found in patients with encephalitis compared to meningitis. Based on our literature review, anti-VZV antibody in the CSF is currently the best diagnostic test for this disease with a reported sensitivity of 98% [8,9].

Our case was challenging in many aspects. First, the immunocom-

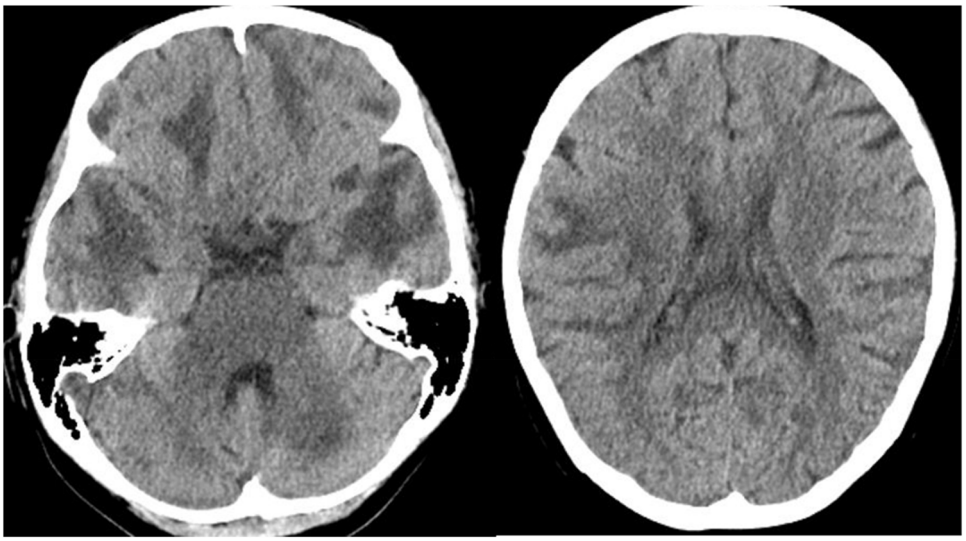

Fig. 2. Computed tomography (CT) of the head showing worsening lucency with mass effect in the bilateral cerebral hemispheres.

promised status of the patient significantly broadened the differential diagnoses. In addition, CSF parameters, besides the lymphocytic pleocytosis, also suggested a bacterial rather than viral CNS infection. Persistently low CSF glucose in the setting of broad systemic antimicrobial therapy was also puzzling. While CSF protein has been reported by Corti et al. [10] to be elevated in VZV meningoencephalitis in the setting of AIDS (median of 2100 mg/dL), whether such high values apply to all patients with diminished immunity is unclear. Moreover, both the angiogram and first two CSF samples tested for VZV PCR were negative. It is possible that the initial negative PCR could have been due to the early timing of CSF collection and small-volume CSF sample as has been described before [7,11]. However, the repeat negative study three days later made us consider other etiologies which inevitably delayed the diagnosis.

To our knowledge, there are no randomized controlled clinical trials available to guide therapy for VZV vasculopathy. The current Infectious Diseases Society of America (IDSA) guidelines recommend acyclovir (category B-III) and adjunctive corticosteroids (category C-III), based mainly on anecdotal cases and expert opinion [12]. However, as noted above, our patient did not respond to this therapy. It is possible that while acyclovir may offer some benefit in patients with unifocal vasculopathy [5], its role in multifocal vasculopathy is unclear. We emphasize that the presence of hemorrhagic brain infarcts in an immunocompromised patient who presents with altered mental status should raise strong suspicision for VZV vasculopathy. The low sensitivity of CSF VZV PCR in this disease entity should be taken into consideration when testing CSF samples for viral DNA. Although a history of recent zoster rash may be helpful in diagnosis, its absence should not exclude further evaluation of this disease.

Conflict of interest

None.

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