

## Varicella-Zoster Virus Reactivation Resulting in Stroke and Progressive Outer Retinal Necrosis: Case Report and Literature Review

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### Abstract

Varicella-Zoster Virus (VZV) may invade the central nervous system during primary infection. With a decline in VZV-specific cell-mediated immunity, VZV reactivates to cause herpes zoster (shingles) as well as CNS manifestations including meningoencephalitis, Ramsay Hunt Syndrome, leukoencephalopathy, transverse myelitis, and stroke. Various ophthalmologic disorders can occur including Progressive Outer Retinal Necrosis (PORN). VZV is the only virus that has been shown to directly invade cerebral arteries and produce focal or multifocal ischemic damage, vessel wall necrosis with arterial dissection, aneurysm formation, and hemorrhagic stroke involving the brain and spinal cord. The classic presentation is contralateral hemiparesis usually resulting from infarction of the ipsilateral middle cerebral artery several weeks after the onset of herpes zoster ophthalmicus. We report a 53-year-old immunocompromised male patient with stroke and PORN after shingles.

**Keywords:** Varicella-Zoster Virus; AIDS; Stroke; MRI; PORN

### Introduction

Varicella zoster virus (VZV), a double stranded DNA virus, is a member of the Herpesviridae family and highly neurotropic in nature [1]. Reactivation of latent VZV leads to herpes zoster (shingles) with characteristic dermatomal rash often complicated by postherpetic neuralgia, meningoencephalitis, myelitis, serious ocular disorders, and VZV vasculopathy [2]. Associated neurologic and ocular deficits may develop without characteristic herpes zoster dermatomal rash [3] which could make early detection in susceptible patient populations difficult and delay preventative neurologic care. VZV vasculopathy is a major complication as it can be a cause of stroke in adults [2]. Of reported VZV vasculopathy cases, the frequency in immunosuppressed patients is 41.9% and ischemic stroke occurs at a rate of 37.1% [1]. Of note, VZV is the only virus that has been shown to directly invade cerebral arteries and produce vasculopathy [4]. Current management is based on intravenous acyclovir with or without corticosteroids; however, the duration of treatment, and the necessity of concomitant use of corticosteroids are not well established [1,5].

We report a unique case of ischemic stroke and retinitis in an AIDS patient having recurrent herpes zoster activation and also review the literature to further explore the underlying pathophysiological mechanism, treatments, and outcomes associated with VZV-associated vasculopathy.

### Case Report

A 53-year-old male presented to the emergency department with right-sided weakness for the past 22 hours. At presentation, the

patient was evaluated with a NIH stroke score of 7. The patient’s past medical history was significant for human immunodeficiency virus (HIV) diagnosed in the 1990s, 3 episodes of recurrent shingles over 3 years, and bilateral vision loss. The patient had no history of hypertension, dyslipidemia, or diabetes. He admitted to a 30-pack-year cigarette smoking history; however, he denied alcohol and drug use. HIV status was believed to be from a deceased female partner. The patient denied history of other sexually transmitted diseases.

**Herpes Zoster History**

Three episodes of herpes zoster shingles had been recorded over the course of 3 years prior to the stroke onset. Episode one occurred 3 years prior to stroke presenting as a “rash on his chest. Episode two occurred 2 years prior to stroke presenting as a “genital rash”. Episode three occurred 2 months prior to stroke presenting as a “rash” involving his right upper extremity. For each episode, the patient was prescribed Valacyclovir and Acyclovir in the emergency department and symptoms resolved.

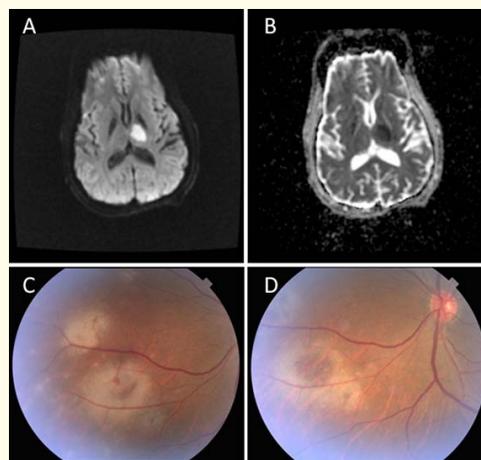
Two months prior to the stroke, the patient was admitted for loss of vision in the left eye and was evaluated by infectious disease and ophthalmology. MRI of the ocular orbit with and without contrast displayed left optic nerve enhancement. The patient was diagnosed with progressive outer retinal necrosis (PORN) secondary to varicella zoster virus (VZV) associated retinitis (Figure C and D). PORN progressed to the right eye one week after left eye onset despite antiviral therapy.

PCR analysis of CSF and bilateral vitreal biopsy confirmed VZV. Quantitative PCR analysis of CSF was negative for cytomegalovirus, but positive for VZV DNA at 1.8 million copies/ml (ref < 500 copies/ml). Blood herpes simplex virus IgM antibody was negative.

A 2-week course of intravenous (IV) Ganciclovir and Foscarnet was started, as well as, two intravitreal Ganciclovir and Foscarnet injections in both eyes. A pars plana vitrectomy with endolaser and scleral buckling was scheduled 2 days after presentation for stroke. The patient was discharged on Valacyclovir and Highly Active Antiretroviral therapy (HAART). On follow up, the CD4 count rose from 3 to 45 cells/ $\mu$ l and the HIV viral load decreased from 35,462 to 81 copies/ml.

**Imaging**

Initial cranial computed tomography (CT) scan without contrast noted left basal ganglia hypodensity involving the genu and posterior limb of the left internal capsule and a portion of the medial thalamus. There was an additional hypodensity involving the right frontal lobe. A subsequent brain MRI showed a 2.2 cm acute infarction of the left thalamus and basal ganglia without intracranial hemorrhage (Figure A and B). Magnetic resonance angiography (MRA) of the neck and carotid arteries demonstrated normal carotid and vertebral arteries.



**Figure:** Brain MRI imaging and retinal imaging: Brain MRI: There are abnormal signal lesions on diffusion weighted images (DWI) (A) and the ADC map (B) compatible with acute infarction involving the left thalamus and basal ganglia measuring 2.2 cm. The progressive outer retinal necrosis (PORN) secondary to VZV retinitis is shown at initial ophthalmology evaluation (C) and 2 months after diagnosis (D).

### **Laboratory and Diagnostic Tests**

Serology for vasculitis, rapid plasma reagin (RPR), Hepatitis B, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), anti-neutrophil antibodies (ANA), and anti-neutrophil cytoplasmic antibodies (ANCA) were negative. HIV serology was positive for HIV-1 RNA with 13,290 copies/ml (ref < 20 copies/ml) and negative for HSV1/HSV2 IgG, Toxoplasma IgM, and Cryptococcal antigen. Blood chemistry showed an LDL of 89 mg/dl and HbA1C of 5.0%. Cardiac echocardiography noted an ejection fraction of 55 - 60% and no evidence of an intracardiac shunt.

### **Management**

The patient responded well to 2 weeks of IV Acyclovir and 5 days of oral Prednisone 1 mg/kg/day. He was discharged on oral Valacyclovir 1000 mg three times daily and HAART therapy along with Atropine and Prednisolone eye drops.

### **Discussion**

Here, we report a case of ischemic stroke and herpetic retinitis occurring in an AIDS patient with recurrent herpes zoster (VZV) activation.

VZV has an initial presentation in childhood as varicella (chickenpox), after which the virus becomes latent in the cranial nerve ganglia, dorsal root ganglia, and autonomic ganglia [2,6]. Advanced age and conditions of immunosuppression such as severe stress and AIDS can result in cell-mediated immunity decline and VZV reactivation to produce herpes zoster (shingles) [2,5,7,8]. Our patient encountered two major complications of herpes zoster reactivation--VZV vasculopathy and progressive outer retinal necrosis.

VZV vasculopathy is believed to be due to nerve and vessel proximity. VZV spreads transaxially often from the trigeminal ganglia where it can reach cerebral arteries [9]. VZV principally infects the arterial adventitia then spreads transmurally to infect all vessel layers resulting in a characteristic granulomatous arteritis pathology [2,10]. Infarctions within the trigeminal nerve distribution or cervical distribution are mostly ischemic [11] and rarely hemorrhagic [12]. Furthermore, recurrent herpes zoster episodes along with complications are rare, but may manifest more often in individuals who are immunosuppressed.

Evidence of stroke was readily demonstrated in our patient. Clinically, our patient developed a focal neurologic deficit of right-sided hemiplegia. Further, head CT without contrast displayed left basal ganglia hypodensity involving the genu and posterior limb of the left internal capsule and portion of the medial thalamus. Subsequent brain MRI showed an acute infarction of the left thalamus and basal ganglia without hemorrhage. Taken together, these findings clearly suggest our patient encountered a stroke involving the distributions of the left middle cerebral artery (MCA). MR angiography showed normal carotid and vertebral arteries further suggesting the pathological lesion occurred principally in the MCA and/or its arterial branches. The patient's HIV/AIDS status and prior multiple recurrences of herpes zoster indicated that VZV-associated vasculopathy could be the cause of stroke.

PCR analysis of CSF for VZV DNA confirmed that the VZV infection had reached the CNS. Vasculitis and other possible microbial causes of stroke were ruled out including CMV, HSV1, HSV2, Toxoplasma, and Cryptococcus by way of serological laboratory analysis. Low LDL levels, normal HbA1c, normal cardiac echocardiography helped to rule out a cardiac embolic event or diabetic vasculopathy. The results of our lab work-up followed current accepted guidelines to use CSF PCR for detection, a sensitive and specific test for VZV DNA [13]. While a biopsy specimen of the MCA demonstrating multinucleated giant cells, Cowdry A bodies, and VZV antigen would have secured a diagnosis of stroke due to VZV it would have been too invasive a procedure [4]. However, the patients confirmed HIV status and history of episodic herpes zoster make VZV the most likely cause.

A notable complication involved in this case is that of progressive outer retinal necrosis (PORN). PORN is characterized by extremely rapid progression, multifocal lesions of the deep peripheral retina with or without macular involvement, and bilateral tendency [14]. Our patient's VZV associated PORN was confirmed by bilateral vitreal biopsy. PORN responds poorly to the mainstay VZV treatment of acyclovir [15]. Thus, we utilized intravitreal ganciclovir and foscarnet injections into both eyes with favorable outcome.

The majority of VZV cases are managed via intravenous (IV) acyclovir; however, the data to support this treatment route is limited. While working up a possible diagnosis of VZV vasculopathy, an immediate course of IV acyclovir, 10 - 15 mg/kg three times daily for a minimum of 14 days should be started [5]. To account for the inflammatory response within cerebral arteries, oral prednisone, 1mg/kg daily for 5 days may be used [5]. No steroid taper is needed. However, never treat with steroids for longer than a week as virus infection can be potentiated [5]. If neurological symptoms post acyclovir treatment continue, oral valacyclovir, 1g three times daily for an additional 1 - 2 months is recommended. Our patient responded favorably to 2 weeks of IV acyclovir and 5 days oral prednisone per current recommendations. To prevent recurrence of neurological symptoms, the patient was discharged on oral valacyclovir as well as HAART therapy to recover immune function.

The discussed case supports the use of PCR analysis of CSF to diagnosis VZV associated stroke and also current recommendations of IV acyclovir and oral steroids for clearing acute flares of VZV activation. Further, the use of intravitreal ganciclovir and foscarnet injections for PORN complication is recommended based on the outcomes of this case.

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### **Author Contributions**

Yongxing Zhou: Resident for patient care, case writing and discussion.

Robert Walker: Case writing and discussion.

David Katz: Attending for eye exam and case discussion.

Roger Weir: Attending supervising patient care and case discussion.

Annapurni Jayam-Trouth: Attending supervising patient care, case writing and discussion.

### **Author Disclosures**

Reports no disclosures.

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