

Herpes zoster ophthalmicus with hemiplegia due to vasculopathy

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Case presentation

The patient is 68 year old white female with a history of type 2 diabetes, hypertension, hyperlipidemia, and congestive heart failure. She is functionally independent. She had chicken-pox as a child but did not receive varicella zoster vaccine. In 2014 she had sudden onset of right facial throbbing headache for 2 days. Subsequently, she developed a rash of varicella zoster viral (VZV) infection in the distribution of right ophthalmic branch of the trigeminal nerve. The rash involves the tip of the nose and the patient was complaining of dizziness and impaired vision. She was seen by the ophthalmologist who put her on antiviral medication because of the threat to her vision.

Two days after the appearance of the rash she complained of headache and weakness of the left side of the body. Neurological examination at that time revealed evidence of left sided stroke in the distribution of the anterior/middle cerebral arteries. A CT scan followed by MRI of the brain confirmed the presence of stroke in the distribution of the MCA at the grey-white matter junction.

A spinal tap along with broader set of diagnostic laboratory tests involving VZV- IgG antibodies, CSF mononuclear pleocytosis, and positive intra-thecal synthesis of VZV-IgG as shown by dissociation of serum to CSF ratio of anti-VZV IgG confirms the diagnosis. Even though, the VZV-DNA was negative. Eventually, a diagnosis of VZV-infection (herpes zoster ophthalmicus with vasculopathy and stroke) was made.

Treatment was started with prednisone 60 mg/day and tapered over 2 weeks, gabapentin 200 mg three times daily, and valacyclovir 500 mg Q12 hrs. For 14 days. The patient made a remarkable recovery with resolution of her neurological deficit, and subsidence of and eventually disappearance of the rash of VZV. Luckily, her vision was not impaired. Three months later she was in a good health, very active in her daily living, and denied post-herpetic neuralgia (PHN).

Discussion

The advent of polymerase chain reaction (PCR) and VZV DNA sequencing along with anti-VZV antibody detection have improved clinical diagnosis of VZV infection. These advances in diagnostic technologies have made identifications of various sequelae of VZV pathology easier. The VZV-vasculopathy including, myelitis, meningo-encephalitis, cerebral ataxia, and cranial polyneuritis can be diagnosed with or without VZV-rash [1].

PCR diagnosis of VZV infection has high sensitivity (95%), and specificity approaching (100%), with no cross reactivity to other herpes viruses [2]. It is rapid, inexpensive, and the specimen can be obtained from CSF, broncho-alveolar lavage, saliva, serum, or whole

blood [3]. VZV-specific antibodies associated with amplification by PCR for VZV-DNA are essential for VZV diagnosis [3]. Post-herpetic neuralgia (PHN) is the most common and dreadful complication from reactivation of VZV. After vaccination the incidence of PHN dropped from 18.5% to 6.0% in patients older than 70 years [4]. When shingles occurs despite vaccination, the extent of the rash and severity of the complications of the virus, like neuropathic pain may be less obvious which confound the diagnosis [4-6]. VZV-DNA and specific anti-VZV antibodies made possible the diagnosis of zoster complications especially in the absence of typical VZV-rash.

Historically, VZV vasculopathy are presented with acute hemiplegia after contralateral herpes zoster ophthalmicus or as arteriopathy in children with varicella [7-10]. The clinical spectrum broadens in recent years after refinement of VZV diagnosis. These pathological phenomena include, vasculopathy (transient ischemic attacks or stroke), multifocal VZV-vasculopathy with temporal artery infection resembling giant cell arteritis (GCA), extra-cranial vasculopathy, aneurysms with and without subarachnoid hemorrhage, arterial dissection etc. as shown in Table 1.

The pathogenesis of VZV-vasculopathy results from reactivation and transmission of the virus through the axons of the nerves to arteritis where productive infection is established. This leads to pathological vascular remodeling with inclusion bodies, multinucleated giant cells, herpes virions and VZV- DNA and antigen deposition in the wall of the vessels, venous sinuses, and dural structure [10-13]. The antigen antibody reaction with recruitment of the CD4+ and CD8+ T- cells, macrophages, and rare CD20+ B-cells culminates in to inflammation of the vessel involved [14]. The culprit vessel infected by the virus would show disrupted internal elastic lamina, a thickened intima by cells expressing actin and myosin heavy chain [10]. All the three layers of the arteries infected by the virus would show inflammatory cell infiltrate. The thickened adventitia is associated with inflammation of the vasa vasorum in the early VZV-vasculopathy [15,16]. These altered pathology lead to arterial caliber irregularities, and contractility that produce aneurysmal dilation, thrombosis, and narrowing of the vessels with attendant cut of the blood supply to the tissue in the territories of the artery involved.

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Table 1. VZV-vasculopathy.

Ischemic and hemorrhagic stroke	VZV-DNA, IgG (+), MRI-ischemic or hemorrhagic lesions in grey-white matter distribution
Multifocal VZV-vasculopathy with temporal artery infection and GCA	GCA-biopsy negative, CSF and TA biopsy may be positive for VZV infection
Extra-cranial vasculopathy	Occlusion, vasospasm, or thrombosis of the extra-cranial arteries.
Aneurysm/hemorrhage	Aneurysms and hemorrhage in the intra-cranial arteries
Arterial dissection and dolichoectasia	Dissection of the carotid arteries associated with VZV-infection and trauma
Cranial neuropathies	Cranial neuropathies after VZV-infection, not uncommon. CNs III, IV, V2,3 and VI (CST), IX, X, XI and XII (ascending pharyngeal artery)
Venous sinus thrombosis	MRI may show filling defects in the cerebral sinuses
Spinal cord infarction/peripheral thrombotic disease	Acute onset myelopathy, diagnosed by diffusion-weighted MRI and CSF virological analysis. Arterial or venous thrombosis of the lower limbs due to VZV-hypercoagulability.

Involvement of different vessels by the virus result in the protean manifestations:

- 1- Ischemic and hemorrhagic stroke.
- 2- Multifocal VZV- vasculopathy with temporal artery infection resembling GCA.
- 3- Inflammation and occlusions of the extra-cranial vessels like common carotid arteries, central retinal artery occlusion, internal carotid artery occlusion, thrombosis, and vasospasm [17,18].
- 4- Arterial dissection and ectasia predisposed by minor trauma [19].
- 5- Cerebral venous sinus thrombosis has been reported as complication of VZV infection [20,21].
- 6- Spinal cord myelopathy and infarction have also been seen with VZV- infection as seen by diffusion-weighted MRI [22,23] and analysis of CSF for VZV infection [24].

Conclusion

VZV-vasculopathy is characterized by protean manifestations as a results of involvement of large and small vessel vasculitis of intra-cranial, extra-cranial vessels, venous sinuses, and cranial neuropathies. VZV-vasculopathy can presented with or without rash and the diagnosis is clinched by CSF specific VZV-IgG, and VZV-DNA by PCR techniques along with imaging of the brain. Confirmation of intra-theal synthesis of anti-VZV antibodies is the key to diagnosis. Treatment of VZV-vasculopathy requires intra-venous acyclovir therapy, the course may be prolonged in immunosuppressed patients.

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