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Herpes zoster ophthalmicus with associated vasculopathy causing stroke

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Abstract

Varicella zoster virus (VZV) is an exclusively human, double-stranded DNA virus. Primary infection causes varicella (chickenpox); later the virus becomes dormant in the dorsal root, cranial nerve, and autonomic ganglia along the entire span of the nervous system, retaining the capacity to reactivate and cause a variety of dermal and neurological complications. Recently there has been increasing recognition, both clinically and epidemiologically, of the relationship between VZV and subsequent strokes. Herein, we describe a case of a previously healthy individual with reactivation of VZV causing herpes zoster opthtalmicus along with devastating multifocal vasculopathy. It is crucial for dermatologists to recognize the dermatomal vesicular eruption in this high risk area to aid in prompt diagnosis in an effort to improve clinical prognosis.

Keywords: varicella zoster virus, stroke, vasculopathy, herpes zoster, herpes zoster opthalmicus

Introduction

Stroke is the fifth leading cause of death in the U.S., killing approximately 130,000 Americans each year [1]. In the last few decades, VZV vasculopathy has been recognized as a broad clinical spectrum and now includes ischemic and hemorrhagic insults, transient ischemic attacks, and cerebral and subarachnoid hemorrhage [2,3]. However, the diagnosis can be challenging since: 1) stroke can happen weeks, months, and even years after zoster reactivation making VZV vasculopathy lower in the differential diagnosis, 2) other vasculopathies also produce the same neurological signs and symptoms, and 3) when viral etiology is suspected, cerebrospinal fluid analysis of VZV DNA is usually the test employed, despite the fact that anti-VZV IgG has higher sensitivity [2, 3]. Owing to all of these factors combined, a dermatologist's ability to quickly recognize and diagnose the dermatomal eruption of VZV in the setting of a stroke of questionable etiology can have a profound impact on a patient's prognosis.

Case Synopsis

A 53-year-old woman with a recent history of multiple ischemic strokes, who was previously healthy, was admitted to the University of Cincinnati Medical Center with new neurological deficits and concern for new posterior circulation strokes. On admission, the patient had worsening left lower extremity weakness with spasticity, right facial droop, right ptosis, and aphasia. She was placed on a heparin drip out of concern for refractory large vessel disease with poor perfusion and continued on her home medications - aspirin 325mg daily and clopidogrel 75mg daily. Previous work up included coagulation studies and homocysteine levels, which were within normal limits. Factor V Leiden was negative and her lipid profile was slightly elevated: cholesterol at 279 mg/dL (desirable level < 150 mg/dL), triglycerides at 166 mg/dL (desirable level < 150 mg/dL), and LDL at 200 mg/dL (desirable level < 129 mg/dL).

One week after admission, the patient developed an ulcerative and crusted eruption on the left forehead extending to the frontal scalp and left cheek without crossing the midline. There were four to six ill-defined

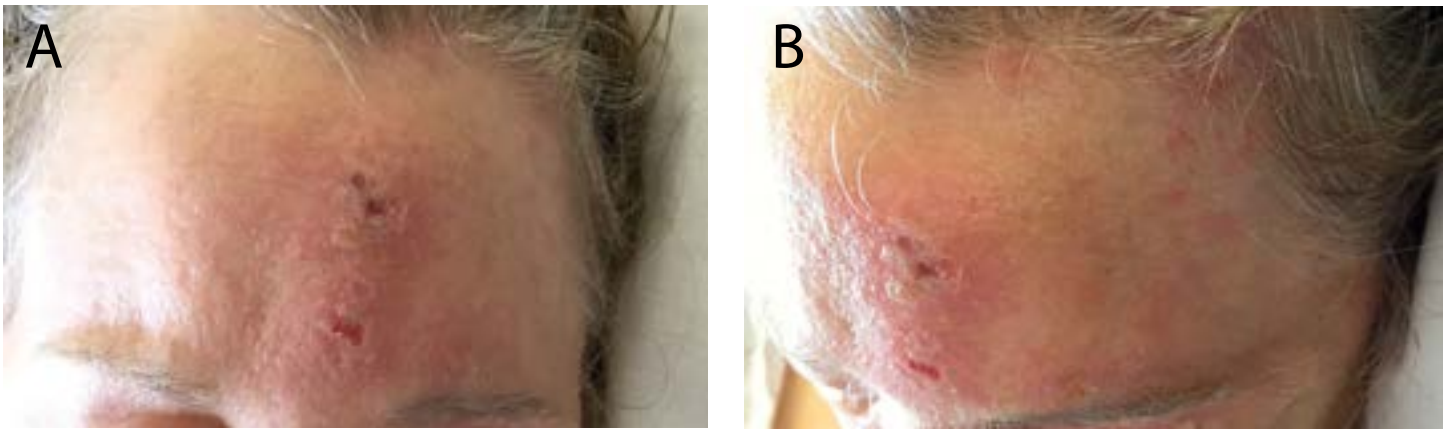

Figure 1. *Clinical photographs revealing several 3-7 mm erythematous macules and papules with focal erosion and crusting on the left forehead extending to the frontal scalp and left medial cheek within the C2-3 dermatome*

erythematous macules and vesicles with focally scalloped ulcerations and overlying thick yellow crust (**Figure 1**). A cutaneous swab of an ulceration revealed positivity for VZV by PCR. On the eight day of her hospital stay, she had cerebral angiography that revealed profound stenosis of the mid-basilar artery, as well as numerous foci of arterial stenosis in both anterior and posterior circulations, suggestive of a vasculopathic process. Given the suspicion for viral etiology based on skin findings, a lumbar puncture was performed and cerebral spinal fluid analysis demonstrated mild elevation in protein but no clear pleocytosis. PCR was positive for varicella DNA; IgM <0.91 mg/L (normal range 0-0.6 mg/L) and IgG were undetected. Additional serologies including HIV, RPR, ANA, C3, C4, EBV, HSV-1, and HSV-2 were all negative as well.

The patient was started on intravenous acyclovir, 10 mg/kg three times a day, for the first two days and then the dose was increased to 15 mg/kg for twelve more days day once the CSF was determined to be positive for VZV. She was also given prednisone 50 mg daily for 5 days. Throughout the admission, she deteriorated clinically to the point that she did not respond to noxious stimuli in any way and did not follow any commands. A repeat MRI on day 16 of her hospital stay demonstrated progressive posterior circulation disease with new large infarcts affecting the brainstem and the left occipital and inferior parietal lobes. The poor prognosis was discussed with the patient's family, who ultimately elected to pursue inpatient hospice care.

Given angiography findings consistent with vasculopathy, dermatomal vesicular eruption positive for VZV, CSF positivity for VZV DNA, and rapid deterioration of a previously healthy low-risk patient, the etiology of our patient's recurrent strokes was most likely VZV vasculitis.

Case Discussion

VZV vasculopathy has been usually described in the literature as ischemic large vessel strokes; however, it is now known that it can affect large and small vessels. In fact, recently an expanded spectrum of stroke caused by VZV has emerged to include aneurysm, subarachnoid and intracerebral hemorrhages, arterial ectasia, and possibly dissection [4]. Our case demonstrates herpes zoster ophthalmicus leading to multiple large and possible small artery strokes. It is estimated that 10-25% of herpes zoster cases are herpes zoster ophthalmicus (HZO) [5]. HZO arises when the dormant virus re-activates along the ophthalmic division of the trigeminal nerve. The virus can damage the eye and adjacent structures by intraneural and perineural inflammation of sensory nerves [6]. Three large epidemiological studies have examined the incidence of stroke after herpes zoster [7, 8, 9].

Analysis of 4.6 million adults from Denmark showed a 127% increased risk of developing stroke in the first 2 weeks after VZV onset, 17% between the first 2 weeks and the first year, and an overall 5% increase compared to those without VZV [8]. Lin et al. specifically looked at the relationship between HZO and stroke - after adjusting for demographics, comorbidities and medications, they found that patients with HZO had a

450% increase risk of developing stroke in a one-year follow-up. They also found a significant difference on the subtype of stroke, with ischemic being more common than hemorrhagic [9]. Finally Kang et al. found that the frequency of stroke after VZV was 1.71% and for HZO specifically 5.83%, according to one-year follow-up data [7]. These studies emphasize the fact that whereas VZV and HZO are frequently seen in a dermatologist's office, it is important for clinicians to be aware of the significant risk of stroke in these patients.

Primary infection with VZV is commonly evidenced in children as varicella, which is typically benign and transient [7]. VZV then becomes dormant in the dorsal root, cranial nerve, and autonomic ganglia alongside the neuraxis waiting to re-activate when VZV cell-specific immunity decreases owing to age or immunocompromised status (e.g. malignancy, AIDS, organ transplantation), [10]. Once it re-activates, it can cause herpes zoster (shingles), which is characterized by painful vesicles in a dermatomal distribution, as well as meningoencephalitis, myelitis, ocular disorders, and vasculopathy [2].

Pathologic examination of VZV vasculopathy reveals the presence of VZV antigen in the adventitia (outermost layer of the artery) in early infection, and in the media and intima later in the course of infection, suggesting a transaxonal spread from ganglion cells to arteries followed by a transmural spread. Once infection reaches the cerebral arteries, it results in a thickened intima, disrupted internal elastic lamina, and scarce smooth muscle cells leading to thrombosis, necrosis, dissection, and even formation of aneurysm [2, 11]. This remodeling continues for months after VZV infection, accounting for the variability of time elapsed between reactivation and stroke [11]. HZO vasculopathy has a predilection for large vessels, as VZV spreads through the trigeminal afferent nerve fibers to the anterior cerebral arteries, middle cerebral arteries, and internal carotid; it also spreads to the skin and forms the classical HZO rash. However, it is important to clarify that VZV reactivation and consequent artery invasion can occur without evidence of a rash (termed zoster sine herpete) [2, 4, 9, 12].

Once VZV vasculopathy is suspected, brain imaging, arteriography, CSF analysis, and ultimate virological confirmation are employed for the diagnosis. Although VZV vasculopathy is a very large and diverse entity, certain findings can help direct the clinician. MRI typically demonstrates cortical and deep abnormalities, seen in both white and grey matter, but predominantly in the grey-white matter junction. Angiographic features include segmental constriction with post-stenotic dilation involving large and small vessels. Pleocytosis and oligoclonal IgG against VZV are the typical CSF abnormality. Lastly, viral confirmation involves PCR detection of VZV DNA or anti-VZV IgG, with the latter being a more sensitive test [12]. Based upon category 3 evidence (opinions of experts, from their clinical experience, studies, or reports) patients are usually treated with intravenous acyclovir. However, duration, dose and adjunctive steroid use require further definition. Prospective studies with larger sample sizes are need to further determine an optimal regimen [13].

This case exemplifies the importance of clinical recognition of VZV. A viral induced vasculopathy is a rare occurrence and is not commonly suspected and tested for, which can delay appropriate treatment. It was because of the dermatologist's suspicion for HZO that this patient underwent a lumbar puncture, which confirmed the etiology of this patient's debilating strokes. Although inpatient diagnosis may require more acute and prompt diagnosis, it is also important for the outpatient dermatologist to be aware of the increased risk of stroke in patients after diagnosing VZV or HZO. Future studies are needed to evaluate the role of treatment of VZV and HZO and to decrease the risk subsequent stroke.

Conclusion

The association between VZV reactivation (especially VZO) and stroke occurrence should not be underestimated. Prompt diagnosis of the clinical findings of VZV and HZO can aid in determining the etiology of a rare vasculopathy allowing initiation of rapid life-saving treatment. Also, being aware of the future risk of stroke in patients commonly seen with VZV and HZO may suggest increased monitoring of these patients.

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