LETTER TO THE EDITOR

To The Editor

Crossed Zoster Syndrome: A Rare Clinical Presentation Following Herpes Zoster Ophthalmicus

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Reactivation of varicella zoster virus (VZV) in the cranial nerve, dorsal root, and autonomic ganglia can lead to unilateral radicular pain and cutaneous dermatomal involvement known as herpes zoster infection. Involvement of the ophthalmic branch (V1) of the trigeminal nerve, or herpes zoster ophthalmicus (HZO), may evolve to include complications such as meningoencephalitis, post-herpetic neuralgia, and contralateral hemiparesis (“crossed zoster syndrome”). Despite increasing reports of delayed contralateral hemiparesis secondary to HZO, the pathogenesis is not well understood. In this report, we review the clinical characteristics and investigations of a case of HZO presenting with posterior reversible encephalopathy syndrome (PRES) and subsequently developing crossed zoster syndrome.

A 75-year-old right-hand dominant female presented to the emergency room in August 2018 with a one-week history of vesicular rash on the tip her nose (“Hutchinson’s sign”) and in the right V1 distribution including the forehead. Her medical history included monoclonal gammopathy of undetermined significance, idiopathic peripheral neuropathy, dyslipidemia, chronic obstructive pulmonary disease, osteopenia, depression, and a 40-pack-year smoking history. While the facial rash had evolved over the preceding week, she was taken to hospital when found by her daughter to be lethargic, in pain, and confused. Neurological examination revealed a right V1 distribution vesicular rash consistent with herpes zoster, mild encephalopathy, and a stable, length-dependent large and small fiber polyneuropathy.

The patient received two doses of IV acyclovir 10 mg/kg at 12-hour intervals due to acute renal insufficiency (eGFR 58 mL/min with Cr 85 μmol/L) but then received 10 mg/kg every 8 hours (eGFR 85 mL/min with Cr 62 μmol/L). Ophthalmological consultation revealed no abnormalities/complications. Initial investigations included (1) magnetic resonance imaging (MRI) demonstrating bilateral subcortical edema in the occipital and parietal lobes, with mild local mass effect and subtle leptomeningeal enhancement in keeping with PRES (Figure 1); (2) lumbar puncture with predominant lymphocytic pleocytosis (WBC 248, reference range 0–5 × 10^6/L; 76% lymphocytes), elevated protein of 1.65 (reference range 0.15–0.45 g/L), negative bacterial and viral cultures, and positive VZV DNA amplification by polymerase chain reaction testing. After 2 days of acyclovir, the patient’s mental status improved to baseline, and she was discharged on oral valacyclovir 2 g three times a day to finish a 10-day course. The patient continued to improve at home over the next week.

Just over 2 weeks after the patient’s initial presentation, she complained of feeling unwell and was emotionally labile, differing from her usual behavior. She had poor oral intake and lethargy and was subsequently brought to hospital. Repeat MRI brain demonstrated a right thalamic lesion (Figure 2), and 8 hours following this, she was found obtunded with left-sided hemiplegia and a right lateral gaze deviation. Emergent CT/CTA head demonstrated an acute right thalamic hematoma, intraventricular extension of the hemorrhage, and secondary hydrocephalus (Figure 2F,G). A diagnosis of VZV small vessel vasculitis with hemorrhagic evolution was made based on clinical and radiological findings. The patient received palliative care at the family’s request and passed away 6 days later.

Following primary infection, VZV may become dormant in the nervous system and in some individuals may reactivate years after initial infection to cause shingles and neurological complications by spreading from the ganglia to cutaneous dermatomes and neural tissues. Delayed contralateral hemiparesis (“crossed zoster syndrome”) is the least common sequelae following HZO, having been described as acute onset of hemiparesis hours to months following resolution of the cutaneous rash. In the largest study of crossed zoster syndrome, the onset between HZO and hemiparesis was 7.3 weeks. In the current case report, we identify a previously independent 75-year-old female with contralateral hemiparesis 20 days following HZO.

The pathogenesis of crossed zoster syndrome is not well understood. The anterior circulation intracranial arteries (middle and anterior cerebral arteries) receive sensory afferents from the ipsilateral trigeminal nerve and retrograde trans-axonal viral spread has been postulated. VZV vasculopathy may cause ischemic or hemorrhagic stroke, or the formation of intracerebral aneurysms which may or may not rupture.

The patient in this report presented with Hutchinson’s sign. This nasal rash of vesicles on the tip or side of the nose, or involving the nasal mucosa, has been previously described, and is associated with an increased risk of complications such as pain, uveitis, and blindness. Hutchinson’s sign has been suggested to predict risk of HZO, but it remains unclear if it also increases risk of VZV-associated vasculitis. Antiviral treatment initiated within 72 hours of VZV cutaneous onset may have benefit, and should be continued for 7 to 14 days. Improvement in hemiparesis has been noted in patients receiving concomitant steroids, but not all patients will benefit from these. Given the possible association with vasculitis, antiplatelet and/or anticoagulation therapy should be considered in patients with early thrombotic changes on imaging.

There are several novel features to the presented case. Our patient initially presented with PRES, and this may be associated with her VZV infection. PRES is most commonly associated with hypertension, significant renal dysfunction, and immunosuppression – risk factors our patient did not have. To our knowledge, PRES has not been associated with VZV in an immunocompetent patient. Furthermore, we present serial imaging documenting the presence of an ipsilateral small vessel vasculitis that immediately preceded the onset of thalamic and ventricular hemorrhage reviewed by two independent neuroradiologists (CJW, RW). It is intriguing to speculate that...
PRES in a patient with HZO could mark impending vascular complications in the setting of VZV infection; however, brain biopsy or autopsy to confirm the diagnosis was not performed which is a limitation of this report.

Contralateral hemiparesis is an uncommon complication following HZO and typically presents weeks to months following resolution of cutaneous and ocular involvement. Prompt diagnosis and management may improve outcome and the associated complications of VZV. Future studies are required to identify biological and imaging markers predictive of the crossed zoster syndrome to recognize patients that could benefit from early intervention. The discovery of PRES at initial presentation of HZO may be one such marker. It is unclear, however, which patients will benefit from the aforementioned therapies to prevent the development and progression of crossed zoster syndrome.

DISCLOSURES

The authors declare that there is no conflict of interest.
STATEMENT OF AUTHORSHIP

AMK and RKK contributed to the drafting and revision of the manuscript. CJW and RW provided neuroimaging and expert interpretation of the findings. KLT provided expert revision of the manuscript.

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