COMPLICATIONS OF VARICELLA ZOSTER INFECTION OF THE CENTRAL NERVOUS SYSTEM

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Introduction

Acute infection with the varicella zoster virus (VZV) is typically a self-limiting childhood illness with few complications. Following an acute infection, VZV becomes latent in cranial nerves and dorsal root ganglia and may reactivate years later to produce herpes zoster (HZ) and postherpetic neuralgia, the most common neurological complication of HZ.[1] The lifetime risk of developing HZ is 20% to 30%, with older patients being the most commonly affected.

Meningoencephalitis (ME) is a serious central nervous system (CNS) complication of VZV infection that requires prompt treatment to prevent a fatal outcome.[2] It is thought to be a direct infection based on the findings of IgM antibodies specific to VZV and a cytopathogenic effect in cerebrospinal fluid.[3] However, recent evidence suggests that this underlying process involves vasculitis that may lead to a delayed stroke-like syndrome and vasculopathy.[4,5]

Infection of the CNS with VZV is not uncommon. A Spanish study demonstrated the presence of VZV DNA in approximately 10% of all cases of aseptic meningitis, ME, and encephalitis.[1,6,7] Myelitis is another fatal CNS complication that may occur several days after the onset of HZ rash.[8-10] We present two patients with neurological complications of VZV, both with varying levels of immune competence.

Case Report 1

A healthy 57-year-old Caucasian female, a competitive marathon runner, presented with a 5-day history of progressively worsening bitemporal and retro-orbital headache, which she described as the "worst headache of her life." This was accompanied by fever and photophobia. Butalbital/acetaminophen/caffeine tablets administered 3 days prior at urgent care did not relieve her symptoms. She had a temperature of 99.4°F with mild neck rigidity and no neurological deficit. No skin rash was noted. Noncontrast computed tomography (CT) scan of the brain was negative, and a basic metabolic panel and complete blood count were normal. A lumbar puncture revealed xanthochromia with a normal opening pressure, white blood cells (WBC) 461 K/mm^3 with 91% lymphocytes, red blood cells (RBC) 23 K/mm^3, protein 182 g/dL, and glucose 45 mg/dL. The patient was treated empirically with vancomycin, ceftriaxone, and acyclovir. CT angiogram of the brain demonstrated a prominent infundibular origin of the right posterior communicating artery concerning for an aneurysm and sentinel bleed. Cerebral angiography, however, was negative. Magnetic resonance imaging (MRI) of the brain revealed mild enlargement of ventricles, sulci, and cisterns without evidence of an acute intracranial process. Viral studies of cerebrospinal fluid (CSF) showed 2,393 VZV DNA copies/mL. She was continued only on acyclovir with progressive improvement and discharged from the hospital to complete 2 weeks of treatment. Complete resolution of symptoms without complications was noted.

Case Report 2

A 27-year-old Hispanic male with a history of advanced human immunodeficiency virus (HIV) infection (CD4 count of 12 cells/mm^3) and noncompliant with highly active antiretroviral therapy presented to the hospital with a 3-week history of altered mental status, bilateral lower extremity weakness, urinary retention, and constipation. He had been hospitalized twice in the preceding month with gastrointestinal symptoms of undetermined etiology. A lumbar puncture performed a week prior to hospitalization at our institution revealed a polymerase chain reaction (PCR) positive for VZV with 6,289 copies/mL. Having refused medical care, he received only 3 doses of intravenous (IV) acyclovir followed by oral prophylactic doses. His past medical history included cytomegalovirus retinitis, *Salmonella*-related mitral valve endocarditis, AIDS-related dementia, and a recent episode of HZ 3 weeks prior to his presenting symptoms. The physical examination revealed complete left-sided vision loss with absent light reflex, 20/40 vision in the right eye, neck stiffness, healed HZ lesions over the left flank, a motor strength of 1/5, and sensory loss in both lower extremities. A normal basic metabolic panel and a serum WBC count of 1.67 K/mm^3 were noted. An MRI of the thoracic and lumbar spine revealed thoracic cord atrophy and diffusely thickened cauda equina nerve roots consistent with HIV myelopathy.

Analysis of the CSF revealed a WBC count of 17 K/mm^3 including 61% monocytes and 38% lymphocytes, with RBC 8 K/mm^3, protein 73 g/dL, glucose 53 mg/dL, and positive VZV PCR with 14, 352 copies/mL. Epstein–Barr Virus PCR was also positive, but copies were not reported. The John Cunningham virus PCR was positive in the blood. The patient received IV acyclovir and foscarnet for ME and suspected VZV transverse myelitis with HIV myelopathy for 2 weeks without any notable evidence of clinical improvement. A repeat CSF analysis done 2 weeks after admission showed a rising VZV PCR of 47,657 copies/mL. In addition, ophthalmologic evaluation of the right eye revealed a new finding of progressive outer retinal necrosis (PORN) consistent with VZV retinitis. Unfortunately, therapy with intravitreal foscarnet injections for the retinitis and a combination of IV foscarnet and acyclovir for ME was unsuccessful, and the patient was discharged to hospice care.

Discussion

These cases indicate that VZV ME can occur in both immunocompetent and immunocompromised patients. Our otherwise healthy competitive runner presented with what she described as the "worst headache of her life," a symptom suggestive of an intracerebral hemorrhage. She presented without a rash, which is in keeping with case reports describing "zoster sine herpete."[11-13] Given her xanthochromia, one could speculate that she had a minor hemorrhage suggesting a possible VZV-associated vasculopathy, which can affect both large or small cerebral arteries.[14,15] Interest-

ingly, VZV can also infect the extracranial temporal, ophthalmic, and retinal arteries, producing symptoms, signs, and laboratory abnormalities identical to those seen in giant cell arteritis.[16]

The viral load in our immunocompetent patient was lower than in our second patient (2,939 vs 6,289). The time course of suspected disease was clearer in the first patient, consistent with evidence that viral loads correlate with severity and duration of neurological disease.[17] It may also explain her rapid response to treatment and progressive improvement. In contrast, the second patient presented with advanced HIV infection with VZV ME and suspected myelitis. Failure to receive consistent therapy until 3 weeks into his course may have contributed to a poor outcome. The striking lack of response to IV acyclovir, manifested by an elevated viral load after 2 weeks of treatment, is consistent with reports of acyclovir-resistant VZV infection after chronic oral acyclovir use.[18,19] His paraparesis with sensory and autonomic dysfunction was suspicious for progressive VZV myelitis with underlying HIV myelopathy. In immunocompetent individuals, postinfectious myelitis resolves spontaneously with or without steroid therapy, while the same can be fatal among the immunocompromised due to spinal cord invasion. Immunocompromised patients also may have ocular manifestations including acute retinal necrosis or PORN, both requiring early diagnosis and aggressive therapy.[20]

These two cases represent the CNS manifestations of VZV infection among individuals at each end of the immunocompetence spectrum. The marathon runner, an immunocompetent host presenting with VZV ME in the absence of typical prodromal symptoms and HZ rash, was responsive to antiviral therapy. Conversely, the immunocompromised patient had an insidiously progressive presentation of the VZV reactivation process, with an aggressive form of disease that was unresponsive to antiviral therapy.

Despite considerable mortality and morbidity related to VZV reactivation, few studies on treatment are currently available. The highly potent attenuated VZV vaccine indicated for prevention of HZ reactivation in individuals aged 60 years and older is reportedly only 50% effective.[21] VZV should be considered in patients with unexplained ME to facilitate early therapy and prevent adverse outcomes.

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References

1. LaGuardia JJ, Gilden DH. Varicella-zoster virus: a re-emerging infection. J Investig Dermatol Symp Proc. 2001 Dec;6(3):183-7.
2. Braun-Falco M, Hoffmann M. Herpes zoster with progression to acute varicella zoster virus-meningoencephalitis. Int J Dermatol. 2009 Aug;48(8):834-9.
3. Auzanneau G, Chagnon A, Morillon M, Verdier M, de Jaureguiberry JP. Isolation of viruses in the cerebrospinal fluid in a case of acute varicella meningo-encephalitis. Presse Med. 1987 Aug 29-Sep 5;16(28):1363-4.
4. Douglas A, Harris P, Francis F, Norton R. Herpes zoster meningoencephalitis: not only a disease of the immunocompromised? Infection. 2010 Feb;38(1):73-5.
5. Petrun B, Williams V, Brice S. Disseminated varicella-zoster virus in an immunocompetent adult. Dermatol Online J. 2015 Feb 22;21(3).
6. de Ory F, Avellón A, Echevarría JE, et al. Viral infections of the central nervous system in Spain: a prospective study. J Med Virol. 2013 Mar;85(3):554-62.
7. Miyazaki Y, Riku Y, Goto Y, Mano K, Yoshida M, Hashizume Y. VZV vasculopathy associated with myelo-radiculoganglio-meningo-encephalitis: an autopsy case of an immunocompetent 66-year-old male. J Neurol Sci. 2008 Dec 15;275(1-2):42-5.
8. Devinsky O, Cho ES, Petito CK, Price RW. Herpes zoster myelitis. Brain. 1991 Jun;114 (Pt 3):1181-96.
9. Kleinschmidt-DeMasters BK, Gilden DH. Varicella-Zoster virus infections of the nervous system: clinical and pathologic correlates. Arch Pathol Lab Med. 2001 Jun;125(6):770-80.
10. Dueland AN, Devlin M, Martin JR, et al. Fatal varicella-zoster virus meningoradiculitis without skin involvement. Ann Neurol. 1991 May;29(5):569-72.
11. Halling G, Giannini C, Britton JW, et al. Focal encephalitis following varicella-zoster virus reactivation without rash in a healthy immunized young adult. J Infect Dis. 2014 Sep 1;210(5):713-6.
12. Jantsch J, Schmidt B, Bardutzky J, Bogdan C, Eckardt KU, Raff U. Lethal varicella-zoster virus reactivation without skin lesions following renal transplantation. Nephrol Dial Transplant. 2011 Jan;26(1):365-8.
13. Kim GU, Ku BD. Varicella zoster virus meningoencephalitis accompanied by rhabdomyolysis without skin eruption. Neurol Sci. 2012 Jun;33(3):623-5.
14. Powell DR 2nd, Patel S, Franco-Paredes C. Varicella-Zoster Virus Vasculopathy: The Growing Association Between Herpes Zoster and Strokes. Am J Med Sci. 2015 Sep;350(3):243-5.
15. Srivastava T, Nagpal K. Herpes zoster meningoencephalitis complicated with peripheral vascular disease: an uncommon presentation of a common disease. Scand J Infect Dis. 2014 Oct;46(10):716-8.
16. Gilden D, Nagel M. Varicella Zoster Virus in Temporal Arteries of Patients With Giant Cell Arteritis. J Infect Dis. 2015 Jul 15;212 Suppl 1:S37-9.
17. Rottenstreich A, Oz ZK, Oren I. Association between viral load of varicella zoster virus in cerebrospinal fluid and the clinical course of central nervous system infection. Diagn Microbiol Infect Dis. 2014 Jun;79(2):174-7.
18. Jacobson MA, Berger TG, Fikrig S, et al. Acyclovir-resistant varicella zoster virus infection after chronic oral acyclovir therapy in patients with the acquired immunodeficiency syndrome (AIDS). Ann Intern Med. 1990 Feb 1;112(3):187-91.
19. Bernhard P, Obel N. Chronic ulcerating acyclovir-resistant varicella zoster lesions in an AIDS patient. Scand J Infect Dis. 1995;27(6):623-5.
20. Franco-Paredes C, Bellehemeur T, Merchant A, Sanghi P, DiazGranados C, Rimland D. Aseptic meningitis and optic neuritis preceding varicella-zoster progressive outer retinal necrosis in a patient with AIDS. AIDS. 2002 May 3;16(7):1045-9.
21. Harte CM, Slattum PW. Recommended immunizations for older adults: a primer for pharmacists. Consult Pharm. 2015 Apr;30(4):210-20.