CLINICAL VIGNETTE

Two Cases of Varicella-Zoster Virus Meningitis

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Introduction

Aseptic meningitis is defined by clinical and laboratory evidence for meningeal inflammation with negative routine bacterial cultures in a person who has not received antibiotics. Meningitis is a rare complication of Varicella-zoster virus (VZV). *"Zoster sine herpete"* or dermatomal pain without rash is characterized by the presence of cerebral spinal fluid (CSF) pleocytosis, isolated VZV polymerase chain reaction in the CSF, and absence of typical skin lesions. We present two patients with VZV meningitis to highlight common findings and clinical differences.

Case Reports

Case 1: A 41-year-old male presented with a diffuse headache that progressively worsened over the day. He described "the worst headache of my life," as throbbing pain that originated from bilateral frontal regions and radiated to the occiput and neck. He denied any neck stiffness, acute vision changes, muscle weakness, numbness, tingling, or facial drooping. He also reported four months with intermittent left eyelid ptosis and a recent resolved sore throat. There was no preceding trauma or known triggers. He denied sick contacts, recent travel, animal exposure, incarceration, or history of herpes. He had not taken his temperature at home and had temperature of 38.3°C in the emergency department (ED). Vitals were otherwise unremarkable. Head motion was limited by headache exacerbation but there was otherwise no nuchal rigidity, focal neurological deficits or rashes. A CT head with angiogram showed no significant intracranial stenosis, aneurysm, intracranial hemorrhage, or mass effect. A lumbar puncture (LP) was performed in the ED. Although opening pressure was not recorded, CSF studies were significant for 560/cmm WBC with 89% lymphocytes, 12/cmm RBC, 116 mg/dL protein, and 45 mg/dL glucose. Complete blood count and basic metabolic panel were normal. He was started on empiric vancomycin and ceftriaxone with CNS dosing, which was stopped after negative CSF bacterial cultures resulted. Acyclovir was not started on initial presentation as he did not have known risk factors. However, on day 2 of hospitalization, CSF, VZV PCR returned positive, and he was started on IV acyclovir following infectious disease consultation. He subsequently developed severe photophobia and worsening headaches that were managed with acetaminophen, gabapentin, and opioids. NSAIDs were initially avoided given the possibility of NSAID associated meningitis in light of his frequent outpatient use. While it is a rare manifestation, NSAID associated meningitis, was initially considered given the paucity of initial positive diagnostic findings, prior to establishing VZV as the underlying etiology. HIV, diabetes, and other immunocompromising states were excluded. No rashes developed throughout his hospitalization. Following one week with improving symptoms, he was transitioned from IV acyclovir to oral valacyclovir 1000mg three times a day to complete a total of 2-weeks treatment with close outpatient follow up with infectious disease.

Case 2: An 82-year-old male with dementia, hypertension, and hyperlipidemia presented with confusion and right sided zoster ophthalmicus. He was diagnosed with shingles involving his right scalp extending to the right periorbital area at an outside hospital. He was transferred for Ophthalmology and management evaluation. He had severe cognitive and functional impairment following a fall one year prior but was able to communicate his needs at his assisted living facility. Staff reported 3 days of increasing generalized weakness and altered responsiveness. On admission, he was minimally interactive, unable to safely swallow food or medications, and functionally bed bound due to his subacute encephalopathy. He was intermittently able to answer simple questions, but at most able to share his name but was otherwise unsure of the time, general location, and reason for his hospitalization. He denied pain or pruritus associated with the vesicular rash overlying his right scalp, extending to his right upper eyelid. He described bilateral blurry vision but was unable to clarify the chronicity of these vision changes. On admission, he had a fever of 38.2°C with otherwise normal vital signs. Labs were notable for Plt 101 x10E3 uL without anemia or leukocytosis, or renal insufficiency. Ophthalmology determined there was no ocular involvement and he was started on started on IV vancomycin, ceftriaxone, and acyclovir with Infectious Disease guidance. Initial attempts at LP were unsuccessful due to inability to maintain a lateral decubitus position as well as spinal surgeries. Six days after initiating empiric therapy LP under fluoroscopic guidance demonstrated 70/cmm WBC with 94% lymphocytes, 14/cmm RBC, 56 mg/dL protein, and 64 mg/dL glucose and positive CSF VZV. Bacterial and other viral CSF cultures were negative. He remained on vancomycin for the superimposed cranial cellulitis. Vancomycin was stopped after development of acute kidney injury with creatinine increasing from baseline 0.87 to 1.79 mg/dL on Day 7 of IV acyclovir. Although the suspected culprit was IV acyclovir despite concurrent IV fluids, vancomycin was also stopped after 6-days of treatment to avoid further renal insufficiency. Creatinine returned to normal after

several days of increased IV fluids up to 4L per day. He finished a 14-day course of IV acyclovir with resolution of his cutaneous lesions. Throughout his hospitalization, his mental status waxed and waned. This was likely due to hospital delirium while in a windowless room in the ED. He improved and was able to return to his prior level of alertness and tolerate his diet with texture modifications. He was discharged to a skilled nursing facility to continue physical and occupational therapy.

Discussion

VZV causes chickenpox (varicella) in children and shingles in the elderly. Immunocompromised patients with HIV, uncontrolled diabetes, psychological stress, and many other causes, can have to reactivation of dormant VZV from spinal ganglia from prior infection. Shingles is typically associated with a painful postherpetic neuralgia which can last up to several months. In Zoster sine herpete, the VZV reaction occurs at the neuronal level without cutaneous involvement.[1,2]

VZV is a cause of aseptic meningitis even in immunocompetent adults, with a greater prevalence in males. The first patient illustrates an otherwise healthy young adult with idiopathic VZV meningitis with rapid recovery. In contrast, the second elderly male's presentation is more typical. Memory T cells responsible for VZV suppression can decline after time and contribute to viral reactivation. This phenomenon explains the higher incidence of shingles with advanced age. Older patients have an increased chance of herpes zoster, and VZV meningoencephalitis involving meningeal and brain parenchyma damage resulting in worse outcomes. VZV meningitis in younger patients may only involve the meninges, with better prognosis.[1-3]

The treatment for VZV meningoencephalitis is IV acyclovir with 8 hour dosing. One common complication is acute kidney injury (AKI), due to intratubular precipitation of relatively insoluble crystals. This usually seen within 12-48 hours of therapy initiation. Prior studies have reported 12-48% of patients with acyclovir induced renal injury.[4] AKI is usually intrinsic although septic patients may be at greater risk to have multifactorial etiologies. It is prudent to administer IV fluids both before and after each dose of IV acyclovir to minimize the risk of renal dysfunction. Nevertheless, as shown in the second case, renal injury may still occur despite hydration. Renal damage associated with acyclovir therapy is usually reversible with timely recognition and intervention. Treatment depends on the severity of renal failure including hydration awareness, induction with a loop diuretic to wash out obstructing crystals, and initiation of dialysis when necessary. Hemodialysis is more effective than peritoneal dialysis in removing acyclovir.[5,6]

Future studies may identify additional preventative benefits, including whether shingles vaccines can decrease neurologic involvement in addition to cutaneous involvement with VZV reactivation. It is generally advised to obtain diagnostic samples with an LP prior to initiating empiric treatment for higher yield micro results. However, obtaining the procedure may be logistically difficult. Further information on whether there is a significant change in false negative results with each additional day of treatment would be informative. If there is a prolonged time range in which false negative results are minimized, clinicians may be more inclined to empirically start VZV meningitis treatment while balancing the risk of renal side effects. Future studies could identify patient subpopulations who would benefit more from increased fluid hydration when receiving IV acyclovir, especially patients with concurrent comorbidities such as congestive heart failure that necessitate prudent fluid administration.

Conclusion

Health care providers should consider meningoencephalitis as part of the infectious evaluation of acute encephalopathy, headaches, or other neurologic deficits. Historically, viruses like VZV have been considered in immunocompromised individuals. However, as in the first case, VZV meningitis also occurs in immunocompetent patients. Renal dysfunction is common with parenteral acyclovir treatment, best mitigated with concurrent fluid administration.

REFERENCES

1. **Alvarez JC, Alvarez J, Tinoco J, Mellado P, Miranda H, Ferrés M, Forero J, Álvarez C**. Varicella-Zoster Virus Meningitis and Encephalitis: An Understated Cause of Central Nervous System Infections. *Cureus*. 2020 Nov 20;12(11):e11583. doi: 10.7759/cureus.11583. PMID: 33364107; PMCID: PMC7749804.
2. **Yan Y, Yuan Y, Wang J, Zhang Y, Liu H, Zhang Z**. Meningitis/meningoencephalitis caused by varicella zoster virus reactivation: a retrospective single-center case series study. *Am J Transl Res*. 2022 Jan 15;14(1):491-500. PMID: 35173869; PMCID: PMC8829630.
3. **Sahra S, Jahangir A, Glaser A, Mobarakai N, Jahangir A**. Case report: aseptic meningitis secondary to varicella-zoster virus (VZV) without an exanthem post MMR vaccination. *BMC Infect Dis*. 2021 Aug 3;21(1):746. doi: 10.1186/s12879-021-06453-5. PMID: 34344345; PMCID: PMC8330204.
4. **Perazella MA**. Crystal-induced acute renal failure. *Am J Med*. 1999 Apr;106(4):459-65. doi: 10.1016/s0002-9343(99)00041-8. PMID: 10225250.
5. **Fleischer R, Johnson M**. Acyclovir nephrotoxicity: a case report highlighting the importance of prevention, detection, and treatment of acyclovir-induced nephropathy. *Case Rep Med*. 2010;2010:602783. doi: 10.1155/2010/602783. Epub 2010 Aug 31. PMID: 20862348; PMCID: PMC2939444.
6. **Lee EJ, Jang HN, Cho HS, Bae E, Lee TW, Chang SH, Park DJ**. The incidence, risk factors, and clinical outcomes of acute kidney injury (staged using the RIFLE classification) associated with intravenous acyclovir administration. *Ren Fail*. 2018 Nov;40(1):687-692. doi: 10.1080/0886022X.2018.1487866. PMID: 30741619; PMCID: PMC6319461.