CLINICAL VIGNETTE

Grave Sequelae of Disseminated Varicella Zoster Virus

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Case

A 67-year-old male presented to the emergency department with bilateral lower extremity weakness and falls.

The patient reported onset of decreased strength in bilateral lower extremities 10 days prior to presentation. He also noted worsening balance while walking, with three mechanical falls without syncope. He reported occasional positional light-headedness, but no chest pain, shortness of breath, cough or fevers. He had no change in upper extremity strength. Past Medical History includes Parkinson disease, type 2 diabetes mellitus with end-stage renal disease, status post-transplant. Two weeks prior he noted a new painful, non-vesicular rash on his right chest wall which was attributed to a new medication, and was now improving.

The patient underwent infectious evaluation, which was negative and neurology was consulted and ordered MRI of the brain, and cervical, thoracic and lumbar spine. MRI brain was unremarkable, but MRI thoracic spine revealed multiple, intramedullary cystic foci in the thoracic cord, without associated enhancement, thought to represent developmental cystic lesions such as intramedullary neuroenteric or ependymal cysts, with neoplastic process less likely. His subacute weakness was attributed to possible worsening of his Parkinson disease, and his carbidopa/levodopa dose was increased. He was discharged to an acute rehabilitation facility (ARU) to undergo aggressive physical therapy.

Following admission to ARU the patient noted progressive bilateral lower extremity weakness and developed fever to 101.4F. He was transferred back to the hospital and re-admitted. Physical exam was notable for right greater than left lower extremity weakness with positive Babinski sign, and bilateral decreased lower extremity sensation. Repeat MRI of the cervical, thoracic, and lumbar spine two weeks after initial imaging now demonstrated progression of T2 hyperintense thoracic cystic lesions with growth and confluence. Neurology and infectious disease services were consulted.

Given the rapid progression of his thoracic lesions and recent fever, infectious/inflammatory causes were felt more likely, though neoplastic, metabolic, or congenital causes were not excluded. The patient underwent broad infectious evaluation including extensive testing for virus: HIV, HTLV-1, enteroviruses, flaviviruses, CMV, VZV, HSV, HCV, EBV; bacteria: TB, syphilis, lyme; fungal: cryptococcus, coccidiodes, histoplasma, blastomycoses and parasitic infections. Additional testing included: RPR, ACE, ESR, CRP, ANA, SSA/SSB, ANCA, RF, Anti-cardiolipin Ab and nutritional deficiency: B12, folate, MMA, homocysteine, copper, zinc, vitamin E. Other diagnostic testing included lumbar puncture, which established diagnosis when cerebrospinal fluid (CSF) PCR returned positive for varicella zoster virus (VZV).

The patient was started on intravenous ganciclovir and switched to intravenous acyclovir after negative CMV PCR. He had weekly lumbar punctures to assess for clearance, but unfortunately remained with persistently positive CSF for VZV despite high dose systemic treatment with acyclovir. Additionally, he developed VZV retinitis and was evaluated by ophthalmology who performed bilateral vitreous taps with intravitreal foscarnet injections.

After five weeks of hospitalization, despite continued parenteral acyclovir, the patient developed acute altered mentation with unresponsiveness. Code stroke was activated and brain MRI showed an acute left basal ganglia infarction. MRA of head and neck raised concern for vasculitis in bilateral MCAs and distal ICA, likely due to disseminated central nervous system VZV vasculitis. The patient required intubation and mechanical ventilation, and was transferred to the intensive care unit. Repeat MRIs identified additional new strokes in the cerebellum and right frontal-temporal areas. Other complications included acute kidney injury, severe pancytopenia, and healthcare associated pneumonia with acute respiratory distress syndrome. The patient remained comatose in the ICU. Following goals of care discussions with his family, he was transitioned to inpatient hospice, and died after palliative extubation.

Discussion

Varicella zoster virus (VZV) is increasingly recognized for serious neurologic complications. This case demonstrates devastating consequences of disseminated VZV leading to myelitis, retinitis and vasculitis with fatal multifocal stroke.

VZV is a human herpesvirus in which primary infection causes varicella (commonly known as chicken pox). The virus remains latent in neuronal ganglia, where no viral replication or

neuronal damage occurs. Immunity to VZV is primarily T-cell mediated even though VZV antibodies are produced following infection.[1] With increasing age and/or immunosuppression, T-cell mediated immunity declines, placing patients at greater risk for VZV reactivation. Reactivation triggers significant viral replication with associated inflammation, ganglionic necrosis and hemorrhage, with multiple potential complications.[2]

When VZV reactivates and travels anterograde to the skin, it causes herpes zoster or shingles, characterized by a painful vesicular rash and potential for post-herpetic neuralgia.[1] Less commonly reactivation of VZV with retrograde neuraxial transmission can cause a myriad of serious complications, including stroke, myelitis, meningoencephalitis, cranial nerve palsies, retinitis, and vasculitis.[3] These sequelae can develop both in the presence or absence of the vesicular rash, and complications can be seen up to four months following the initial zoster rash.[4]

VZV complications can present with varying symptoms. Meningitis or encephalitis can present with headache, fever, and altered mental state. VZV myelopathy can present with spastic paresis with muscle distribution based on spinal nerve region, with possible sensory or autonomic involvement.[3] Severe cases, often in immunocompromised individuals, can involve spinal cord invasion manifesting as gradual myelopathy progressing to a fatal myelitis. VZV is also a principal cause of acute retinal necrosis, and can lead to precipitous vision loss as well as retinal detachment. Prompt anti-viral treatment is essential.[3]

Stroke and VZV vasculopathy are rare devastating complications, and can occur in both primary VZV infection or reactivation. Studies report zoster is an independent risk factor for stroke, wth significantly increased short term stroke risk: 1.5 – 2-fold increased stroke risk within the first 3 months of zoster infection as well as increased long-term risk. Patients with herpes zoster ophthalmicus had 45 times greater one-year risk of stroke, with 8.1% absolute risk compared to controls.[2,4]

Patient with VZV vasculopathy can present with ischemic or hemorrhagic stroke, aneurysm, carotid dissection, or arterial occlusion. VZV vasculitis can affect both large and small cerebral arteries with stenosis and post-stenotic dilatation.[5] Histological examination of affected arteries in VZV vasculopathy reveals inflammatory cells including T cells, macrophages, and neutrophils in the adventitial layer of the vessel wall as well as intimal thickening suggestive of vascular remodeling.[5]

VZV vasculitis is diagnosed by abnormal MRI brain imaging, in conjunction with positive viral DNA or anti-VZV antibodies in cerebrospinal fluid. CSF studies often show a mononuclear pleocytosis. Positive CSF VZV PCR is diagnostic; however, it may result negative as early as 14 days after initial infection. Anti-VZV CSF IgG is a more sensitive diagnostic test, as it can remain positive much longer.[4] Radiographically, gray-white matter junction infarctions are characteristic of VZV vasculitis, and there is a somewhat greater predilection for deep rather than cortical infarcts. Strokes are often multifocal. MR angiography is also key to diagnosis, with characteristic stenotic and post-dilation vessel findings as seen above as well as vessel wall enhancement.[4]

Patients with VZV vasculitis or other neurologic complications due to VZV should be promptly treated with intravenous acyclovir. A minimum 14-day course is recommended, but prolonged therapy for an additional two to four weeks can be administered in severe or progressive cases. Patients can also be treated with a short five-day course of prednisone (1 mg/kg), although its benefit is uncertain, with no published randomized controlled trials.[1] Empiric treatment should be initiated while awaiting confirmatory testing in patients with suspected VZV vasculopathy.

Immunocompromised patients are at greatest risk for VZV reactivation and complication. These include patients with HIV, malignancy such as leukemia or lymphoma, as well patients on chronic immunosuppression for rheumatologic conditions or organ transplantation. Specifically in renal transplant patients, a single center study reported a modest, 3.5% prevalence of VZV infection, with the vast majority (87%) of VZV infections occurring within the first year post-transplantation. Seventy percent of patients had recently increased immunosuppression prior to VZV diagnosis.[6]

Prevention of VZV reactivation and sequelae can be achieved with administration of the zoster vaccine. Studies report both endogenous and exogenous exposure to VZV also boost immunity. The Shingles Prevention Study demonstrated the efficacy of live-attenuated zoster vaccine (Zostavax) in a large, randomized, double-blind, placebo-controlled study published in 2005. The vaccine reduced the incidence of zoster by approximately 50% and post-herpetic neuralgia by 65%.[7] Subsequent studies have shown that the vaccine is effective in preventing zoster for up to ten years following vaccination. In 2018, an inactivated recombinant zoster vaccine (Shingrix) became available that can be administered to immunocompromised groups (unlike Zostavax) while also providing vaccine efficacy for a longer time period.[8] The vaccine is currently recommended for all adults age 50 and above and for those above 18 who are immunosuppressed.

Conclusion

Reactivation of varicella zoster virus (VZV) commonly results in herpes zoster, but can also include potentially devastating neurologic complications including stroke, myelitis, meningoencephalitis, and vasculitis. Immunocompromised patients are at greatest risk, and evaluation with MRI and lumbar puncture are essential for diagnosis. Treatment involves prompt initiation of IV acyclovir. Vaccination with the recombinant zoster vaccine should be recommended for eligible adults.

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