

Clinical Reasoning: A 56-year-old woman with acute vertigo and diplopia

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Section 1

A 56-year-old woman with a recent diagnosis of primary light-chain (AL) (lambda type) amyloidosis complicated by mild infiltrative cardiomyopathy and autonomic neuropathy had sudden onset vertigo and diplopia. She also had a history of hyperlipidemia and hypothyroidism. The diplopia was binocular and worsened on rightward gaze. The patient denied headache, fever, neck stiffness, photophobia, confusion, tinnitus, or impaired hearing. Prior to presentation, she had completed her third cycle of chemotherapy at an outside facility for AL amyloidosis with bortezomib, lenalidomide, and dexamethasone and had come to our facility for a second opinion regarding her amyloidosis when this event happened. Her other medications included aspirin, atorvastatin, levothyroxine, spironolactone, torasemide, midodrine, calcium, and vitamin D. She did not smoke or use alcohol. Her vital signs included a temperature of 36.4°C, blood pressure 109/82 mm Hg, and heart rate 80. Her general examination revealed cachexia and bilateral pitting edema. Her neurologic examination revealed a right sixth cranial nerve palsy, direction-changing nystagmus, mild right-sided dysdiadochokinesis, and mild weakness (Medical Research Council grade 4 of 5) of the deltoids and iliopsoas bilaterally; head impulse test was negative and there was no skew deviation. Her mental status, gait, reflexes, and sensory examination were within normal limits. A skin examination revealed a scattered pustular right-sided rash in the peri-auricular region, neck, chest, and thigh, which the patient mentioned was of new onset. There was no periorbital purpura or macroglossia.

Questions for consideration:

1. What is the localization?
2. What is the differential diagnosis?

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Section 2

The constellation of diplopia, sixth nerve palsy, direction-changing nystagmus, and negative head impulse test clinically suggested a central rather than peripheral etiology for vertigo. The most likely single localization was the pons. The absence of a horizontal gaze palsy favored a fascicular rather than nuclear sixth nerve palsy. The differential diagnosis included the following:

1. Ischemic stroke (e.g., basilar thrombosis, lacunar, cardioembolic [given cardiomyopathy])
2. Posterior fossa hemorrhage (in setting of thrombocytopenia)
3. Infectious rhomboencephalitis (e.g., listeria, other etiologies [viral, fungal])
4. Paraneoplastic/autoimmune rhomboencephalitis
5. Toxic/metabolic encephalopathy (e.g., medication-induced, osmotic demyelination)
6. Demyelination (e.g., multiple sclerosis)

The differential diagnosis of an acute neurologic episode in a patient undergoing chemotherapy for malignancy should include a direct toxic effect of the chemotherapy, an indirect consequence of the treatment (e.g., infection from the associated immunosuppression), direct neurologic involvement of the neoplasm, an indirect consequence of the neoplasm, or a paraneoplastic phenomenon. The acuity suggested a vascular etiology, and initial imaging with CT head was normal excluding a posterior fossa hemorrhage, which the patient was

at risk for given that initial blood tests revealed a thrombocytopenia (platelets 114,000/mm³; normal, 150–450). An EKG revealed normal sinus rhythm and a cardiac MRI 3 months prior revealed a preserved ejection fraction of 59%; AL amyloidosis increases the risk of ischemic stroke, often from a cardioembolic source.¹ CT angiogram was normal excluding a large vessel occlusion (e.g., basilar thrombosis), a neurologic emergency important to exclude in the setting of an acute brainstem syndrome. An MRI head without contrast was undertaken 18 hours after onset to assess for a small infarct in the brainstem, but was without definitive abnormality and excluded other inflammatory disorders (e.g., multiple sclerosis). Paraneoplastic syndromes are not typically encountered with AL amyloidosis and were believed to be unlikely. Quadripareisis and brainstem findings could suggest osmotic demyelination but a recent serum sodium had been normal, and the weakness was proximal, suggesting myopathy from recent steroid use as a more likely cause. Thiamine deficiency is another possibility in a cachectic patient with diplopia, but the ataxia was mild and appendicular (rather than truncal). The presence of a rash and vertigo led to investigations for alternative etiologies, although testing serum thiamine level and empiric administration of thiamine may have been reasonable while investigations were ongoing.

Question for consideration:

1. Does a negative MRI with diffusion-weighted imaging exclude a small brainstem stroke?

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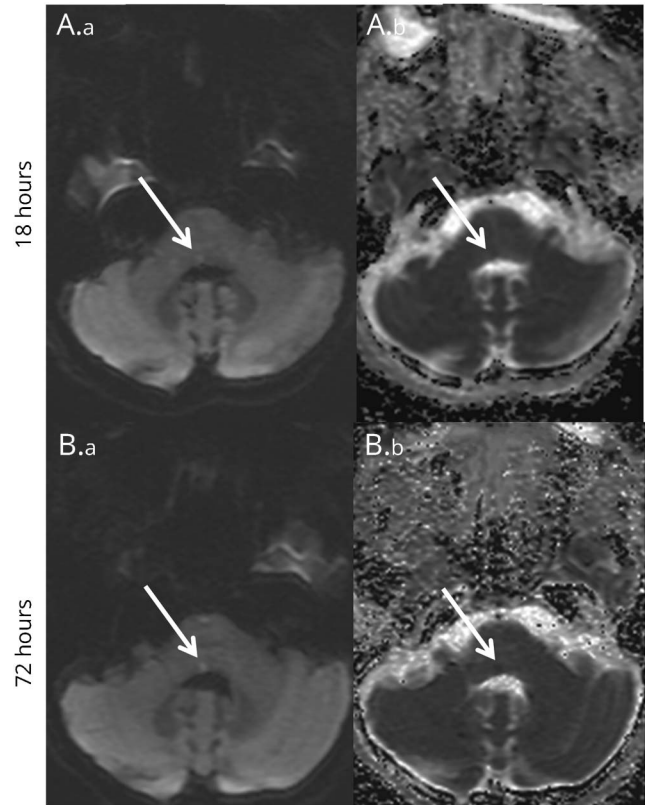
Section 3

Diffusion-weighted imaging (DWI) with MRI has limited sensitivity for small brainstem strokes particularly within the first 48 hours after onset.² This may be due to insufficient signal to noise ratio, poor spatial resolution, magnetic susceptibility artifacts in the brainstem, or location of the imaging slice. In our patient, the first MRI with DWI and apparent diffusion coefficient sequences was performed less than 24 hours after symptom onset and reported to be without definitive abnormality. Repeat MRI with gadolinium performed at 72 hours after onset showed a small area of restricted diffusion in the dorsal pons adjacent to the fourth ventricle without gadolinium enhancement (figure); in retrospect, subtle restricted diffusion may have been present on the initial MRI (A1 and A2, arrows). The infarct was in the region of the right sixth cranial nerve nucleus and its pathway within the dorsal pons.

Questions for consideration:

1. What is the diagnosis and how was it confirmed?
2. How could this have been prevented?

Figure MRI head



MRI head with diffusion-weighted imaging (A.a, B.a) and apparent diffusion coefficient (A.b, B.b) at 24 hours (A.a, A.b) and 72 hours (B.a, B.b) shows a focal area of restricted diffusion (B.a, B.b: arrows) that was not definitively initially apparent (A.a, A.b: arrows).

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Section 4

On initial presentation, a scattered pustular rash was noted on the right side. A swab from a right neck lesion had a positive varicella-zoster virus (VZV) PCR. The presence of disseminated VZV in an immunocompromised host concomitant to the neurologic onset, the known association of VZV with vasculopathy, the MRI appearance favoring small vessel disease rather than embolism (single small infarct in a deep location without other infarcts), and the preserved ejection fraction led us to undertake a lumbar puncture as the next diagnostic step; however, obtaining a transesophageal or transthoracic echocardiogram would have been a reasonable alternative to assess for a cardioembolic source. CSF analysis revealed 350 white blood cells/mm³ (normal, 0–5) with a lymphocytic predominance (86%), 127 red blood cells/mm³, a protein of 186 mg/dL (normal 0–35), and glucose of 34 mg/dL. VZV PCR was positive in CSF. The final diagnosis was disseminated VZV (based on skin involvement of multiple dermatomes) complicated by nervous system involvement with VZV vasculopathy the presumed mechanism of the pontine infarct. The patient was placed on IV acyclovir 10 mg/kg every 8 hours for 21 days. Four days later, she developed a right peripheral facial nerve palsy and prednisone 60 mg/d for 7 days was recommended after multidisciplinary discussion between infectious disease and neurology teams. The ipsilateral right facial nerve palsy may have been from extension of the pontine infarct as the facial nerve in its initial course wraps around the sixth nerve nucleus and closely approximates the sixth cranial nerve before continuing ventrolaterally to emerge from the lateral pons. Alternative explanations included the accompanying brainstem encephalitis or an extrapontine facial nerve mononeuropathy.

Many studies have shown a significant increase in VZV reactivation in bortezomib-treated patients with rates of up to 40% reported.³ Therefore, antiviral prophylaxis with valacyclovir or acyclovir is generally recommended in those receiving bortezomib. One study compared acyclovir 400 mg once daily to 3 times daily dosing and both regimens were shown to protect from the risk of VZV reactivation.⁴ Our patient did not receive VZV prophylaxis during her bortezomib use at the outside facility; if utilized, it may have prevented the development of disseminated VZV.

Discussion

With increasing use of novel chemotherapeutics for hematologic and other malignancies, it is important for neurologists to be aware of the potential for direct and indirect neurologic toxicity and understand how to prevent such complications. This case serves as a reminder of the potential for VZV to cause vasculopathy and illustrates an indirect neurologic complication of bortezomib.

Bortezomib is a selective and reversible proteasome inhibitor that prevents degradation of ubiquitinated proteins. This mechanism of action promotes apoptosis and thus it has shown benefit in a variety of hematologic malignancies. Bortezomib causes indirect inhibition of nuclear factor- κ B (NF- κ B), which controls DNA transcription, cytokine production, and cell survival. Activation of the NF- κ B pathway causes a cellular antiviral response, including production of α/β -interferon, cytokines, and other proteins that restrict viral infection; this pathway's inhibition may explain the risk of VZV reactivation with bortezomib.⁵

Following primary VZV infection, the virus becomes dormant in ganglionic neurons. It reactivates later due to decreased VZV-specific cell-mediated immunity that occurs with aging or, as in this case, in the setting of immunosuppression. VZV reactivation can have many neurologic manifestations including zoster (shingles), herpes zoster ophthalmicus, meningitis, encephalitis, ventriculitis, myelopathy, cerebellitis, retinal necrosis, or limb paresis.^{6,7} VZV vasculopathy is thought to arise from direct infection of the large or small cerebral blood vessels resulting in thrombosis, necrosis, dissection, or aneurysms.⁷ VZV vasculopathy can occur at any age and its frequency may be on the increase with the availability of novel therapeutics that particularly predispose to VZV reactivation. Diagnosis of VZV vasculopathy can be difficult as magnetic resonance angiography, CT angiography, or conventional angiogram are negative in up to 30%, possibly due to the isolated small vessel vasculitis that occurs in over a third of cases.⁸ Detection of VZV DNA in CSF by PCR helps confirm the diagnosis but CSF VZV serology (immunoglobulin G and M) is more sensitive particularly in those without immunosuppression or a delayed presentation. Acyclovir is the treatment of choice (10 mg/kg) each 8 hours \times 14–21 days and some advocate using concomitant oral steroids, as we did.

Author contributions

R. Sharma: drafting manuscript, acquisition of data, analysis and interpretation. Dr. Chakraborty: analysis and interpretation, critical revision for important intellectual content. Dr. Buadi: analysis and interpretation, critical revision for important intellectual content. Dr. Beam: analysis and interpretation, critical revision for important intellectual content. Dr. Pureza: analysis and interpretation, critical revision for important intellectual content. Dr. Pagani-Estevez: analysis and interpretation, critical revision for important intellectual content. Dr. Flanagan: acquisition of data, analysis and interpretation, critical revision for important intellectual content, study supervision.

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Disclosure

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References

1. Zubkov AY, Rabinstein AA, Dispenzieri A, Wijdicks EF. Primary systemic amyloidosis with ischemic stroke as a presenting complication. *Neurology* 2007;69:1136–1141.
2. Edlow BL, Hurwitz S, Edlow JA. Diagnosis of DWI-negative acute ischemic stroke: a meta-analysis. *Neurology* 2017;89:256–262.
3. Chanan-Khan A, Sonneveld P, Schuster MW, et al. Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. *J Clin Oncol* 2008; 26:4784–4790.
4. Pour L, Adam Z, Buresova L, et al. Varicella-zoster virus prophylaxis with low-dose acyclovir in patients with multiple myeloma treated with bortezomib. *Clin Lymphoma Myeloma* 2009;9:151–153.
5. Jones JO, Arvin AM. Inhibition of the NF-kappaB pathway by varicella-zoster virus in vitro and in human epidermal cells in vivo. *J Virol* 2006;80: 5113–5124.
6. Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. Neurologic complications of the reactivation of varicella-zoster virus. *N Engl J Med* 2000;342:635–645.
7. Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. *Lancet Neurol* 2009;8:731–740.
8. Nagel MA, Cohrs RJ, Mahalingam R, et al. The varicella zoster virus vasculopathies: clinical, CSF, imaging, and virologic features. *Neurology* 2008;70:853–860.

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