Clinical Reasoning:

An 83-year-old woman with progressive hemiataxia, tremor, and infratentorial lesions

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SECTION 1

An 83-year-old woman was hospitalized with 6 weeks of progressive left hand incoordination, dysarthria, and gait ataxia, followed by oscillopsia, dysphagia, and left upper limb tremor. She denied cognitive decline, headaches, diplopia, and sensory or systemic symptoms. Ten years previously, she had been diagnosed with locally invasive intraductal breast cancer and treated with lumpectomy, radiation, tamoxifen, and letrozole without recurrence. She denied tobacco or alcohol use. There was no family history of neurologic disease.

Results of the general medical examination were unremarkable. Her mental status was normal, although she had severe cerebellar dysarthria. On

cranial nerve examination, visual acuity degraded during attempted reading. She had saccadic pursuits and gaze-evoked, rebound, and downbeat nystagmus, without ophthalmoparesis. Saccades had a normal latency and velocity but were inaccurate. She had a left upper limb tremor and slight head tremor (videos 1–3 on the *Neurology*[®] Web site at www.neurology.org). Strength, sensation, and tendon reflexes were normal, with flexor plantar responses. She had significant dysmetria, dysidiadochokinesis, and rebound of the left limbs. Her gait was wide-based and ataxic.

Questions for consideration:

1. What are the findings displayed in the videos?
2. What is their localization?

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(A) Initial MRI scan showed increased signal intensity in the left medial cerebellum and a subtle crescent-shaped hyperintensity in the left middle cerebellar peduncle (arrow). (B) At 6 weeks, there was significant expansion of the crescent-shaped lesion (arrow) with extension of hyperintensity into the right pons and midbrain. (C) At 20 months, there was atrophy of the cerebellar vermis and hemispheres, with left greater than right. There was also increased signal intensity in the brainstem and caudal right cerebral peduncle with associated atrophy. No mass effect, gadolinium enhancement, or hypothalamic abnormality was seen on any of the studies.

SECTION 2

Video 1 demonstrates bilateral saccadic hypermetria, with macrosaccadic oscillations, which may be due to a fastigial nucleus lesion. Videos 2 and 3 illustrate a low-frequency kinetic > postural > rest tremor (i.e., Holmes tremor), which localizes near the red nucleus.

Normal or negative blood test results included complete blood count (absolute lymphocytes 1,535 cells/mm³), chemistry panel, thyroid function, Lyme titer, HIV, vitamin E, anti-GAD₆₅ antibody, antinuclear antibody, paraneoplastic panel (anti-Hu, Ma1, Ma2, Yo, Ri, CV2, and Zic4), and antibodies to anti-Ro, anti-La, gliadin, endomysium, and tissue transglutaminase. Brain MRI performed on initial presentation was reported as normal, but in retrospect showed subtle abnormalities (figure, A). CSF revealed 5 white blood cells (WBCs)/mm³ (3 lymphocytes, 1 neutrophil, and 1 monocyte), protein 96 mg/dL, glucose 58 mg/dL, and 3 oligoclonal bands absent in serum, with negative results for a Lyme

titer, bacterial culture, and cytology. Results of mammography were negative. Chest/abdomen/pelvis CT showed biapical lung lesions, indicating a mass or scarring. Fluorodeoxyglucose PET showed regions of increased activity in the lung and colon, but subsequent biopsy results were negative. Hyponatremia (nadir 119 mmol/L) developed 2 months into the illness, spontaneously resolving after several weeks. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) was the suspected cause of hyponatremia. A paraneoplastic syndrome was considered, and after the MRI scan, methylprednisolone (1 g) was given for 3 days with no improvement. The brainstem and cerebellar MRI abnormalities were more clearly evident 6 weeks later (figure, B).

Questions for consideration:

1. What is the differential diagnosis of a brainstem-cerebellar syndrome, with or without tremor, associated with multifocal T2-hyperintense infratentorial lesions?
2. What additional CSF studies would you perform?

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Although the subacute onset, brisk progression, and oligoclonal bands suggest an inflammatory, autoimmune, or infectious etiology, the broader differential diagnosis includes neurodegenerative, neoplastic, and vascular conditions. Cerebellar-type multiple system atrophy and fragile X–associated tremor/ataxia syndrome cause insidiously progressive ataxia and intention tremor, sometimes with cerebellar peduncle T2 hyperintensities. The brain MRI was inconsistent with brain metastases or strokes. CNS lymphoma typically shows contrast enhancement on MRI and hypermetabolic activity with PET imaging, although brain biopsy remains the gold standard for diagnosis. Although Sjögren syndrome may rarely present with cerebellar ataxia, the history does not support Behçet disease or systemic lupus erythematosus. CNS Whipple disease and neurosarcoidosis may produce brainstem-cerebellar and hypothalamic dysfunction (e.g., SIADH). A brainstem syndrome may result from *Listeria monocytogenes*, *Borrelia burgdorferi*, herpesviruses, enterovirus 71, and JC virus (JCV) infection. The diagnosis of Bickerstaff brainstem encephalitis requires encephalopathy or pyramidal tract signs. A paraneoplastic process was suggested by the history of breast cancer, relatively rapid disability, and hyponatremia. As in multiple sclerosis (MS), progressive multifocal leukoencephalopathy (PML) may cause brainstem-cerebellar dysfunction and Holmes tremor.^{1,2} Our patient's advanced age at onset and crescent-shaped cerebellar lesion favor PML over MS.³

Repeat CSF analysis showed 13 WBCs/mm³ (8 lymphocytes, 2 neutrophils, and 3 monocytes), pro-

tein 78 mg/dL, and glucose 135 mg/dL; negative PCRs for herpes simplex virus (HSV), varicella zoster virus (VZV), and *Tropheryma whipplei*; and negative HSV, VZV, and cytomegalovirus immunoglobulin (Ig) G. PCRs were positive for JCV (24,272 copies/mL) and Epstein-Barr virus (EBV) (882 copies/mL, normal <200 copies/mL). The CD4 count was 141 cells/mm³ (absolute lymphocytes 224) 3 weeks after steroids and normalized by 8 weeks (780 cells/mm³). IgM was deficient (13 mg/dL [normal 56–357 mg/dL]), with normal IgA and IgG levels.

Her symptoms progressed for 6 months before stabilizing, leaving the patient with persistent dysarthria, tremor, and left-sided incoordination. Her functional status, including her ability to swallow and ambulate, later showed modest improvement with time. Mirtazapine, a serotonin receptor antagonist, which may block JCV cell entry, was started 9 months into the disease. IgM replacement was not given. A follow-up lumbar puncture was declined. Repeat MRI done at 20 months (figure, C) showed atrophy of the left cerebellar hemisphere extending to the brainstem and right cerebral peduncle. Our patient's survival was attributed to her relatively normal underlying immune status, with a detectable T-cell response against JCV in her blood.

Questions for consideration:

1. What are typical risk factors for PML?
2. What other JCV disorder might the patient have?
3. What is the significance of the elevated CSF EBV PCR?

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SECTION 4

PML is due to JCV infection of oligodendrocytes and astrocytes, primarily in hosts with impaired cellular immunity. It typically presents subacutely with visual, motor, sensory, cognitive, and gait dysfunction, whereas tremor is rare. MRI reveals asymmetric subcortical and cortical U-fiber T2 hyperintensities. The posterior fossa is often affected but rarely selectively.⁴ Involvement of glial cells within gray matter structures, such as the thalamus, basal ganglia, and cortex, is not uncommon. Ninety percent of lesions are nonenhancing, with minimal or no mass effect. In contrast, enhancement is common when PML occurs in the context of an immune reconstitution inflammatory syndrome (IRIS).⁵ Excluding PML-IRIS, CSF in PML is typically normal, although mild elevations in cell count and protein may be seen. CSF JCV PCR has a specificity of ~95%, but sensitivity varies, depending on the population tested (58%–95%). Brain biopsy may be required in CSF JCV PCR–negative patients.

Risk factors include HIV/AIDS, hematologic malignancies, organ transplantation, chronic inflammatory diseases, immunotherapies (e.g., natalizumab), idiopathic CD4⁺ lymphocytopenia, and, rarely, common variable immunodeficiency (CVID).⁶ Our patient's transient lymphopenia seemed to be due to steroids and acute medical illness.⁷ Adult-onset selective IgM deficiency has been associated with particular infections, but not PML. Occasionally chronic disease or advanced age is the only predisposing factor.⁸ Our patient possibly also had JCV cerebellar granule cell neuronopathy, a condition that eventually leads to cerebellar atrophy (figure, C).⁹

The elevated EBV PCR may reflect asymptomatic reactivation due to JCV infection. Alternatively, it may indicate a superimposed EBV encephalitis, which can range from a restricted brainstem encephalitis to a widespread meningoencephalomyeloradiculitis, which may include SIADH.¹⁰ Our patient's mildly elevated CSF cell count and protein may also support the possibility of an additional CNS infection such as EBV. EBV serology would have been necessary to provide definitive evidence for or against active infection. Elevated EBV PCR in patients with HIV/AIDS or recipients of organ transplants supports the diagnosis of a CNS lymphoproliferative disorder. Because hypothalamic dysfunction has not been reported in PML, the cause of hyponatremia in our patient remains uncertain.

PML can thus be entirely infratentorial and may rarely occur without overt immunosuppression. The contribution of IgM deficiency remains unclear, although it could be a *forme fruste* of CVID. A crescent-shaped cerebellar lesion may be a clue to the diagnosis.

AUTHOR CONTRIBUTIONS

K.A., I.J.K., and D.S. drafted/revised the manuscript. I.J.K. analyzed or interpreted the data and contributed vital reagents, tools, and patients.

DISCLOSURE

Dr. Aquino reports no disclosures. Dr. Koralnik has served on scientific advisory boards for Roche, GlaxoSmithKline, and Merck Serono; serves on the editorial board of *Journal of Neurovirology*; receives publishing royalties from UpToDate; has served as a consultant for Bristol-Myers Squibb, Ono Pharmaceutical Co. Ltd., Merck Serono, Antisense Therapeutics Limited, Alnylam Pharmaceuticals, Roche, and GlaxoSmithKline; and receives research support from Biogen Idec, the Neuro-AIDS research consortium, and the NIH. Dr. Silvers has received research support from Teva Pharmaceutical Industries Ltd. for neurology resident education.

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