RESIDENT & FELLOW SECTION

Clinical Reasoning: A 67-Year-Old Woman With Progressive Diplopia, Vertigo, and Ataxia

Marissa Sakoda, MD, Kasra Sarhadi, MD, MPH, P. Annie Weisner, MD, PhD, Shannon Tierney, MD, and Yujie Wang, MD

Correspondence
Dr. Sakoda
marisses@uw.edu

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Section 1

A 67-year-old right-handed woman presented with progressive dizziness and nausea. She had a history of high-grade serous ovarian carcinoma with extension into the colon, diagnosed one and a half years prior. She had previously undergone chemotherapy and sigmoid resection with total abdominal hysterectomy and bilateral salpingo-oophorectomy. She also had a history of type 2 diabetes mellitus complicated by peripheral neuropathy.

She reported several months of progressive dizziness and imbalance, which acutely worsened a few days before presentation. Her dizziness was described as a room-spinning sensation and resolved when she closed her eyes. She also reported new-onset horizontal diplopia and oscillopsia, which abated with closure of the right eye. In addition, she complained of right ear fullness without tinnitus.

On neurologic examination, she had multiple oculomotor abnormalities including limited abduction of the right eye, right-beating nystagmus with right gaze, and vertical nystagmus with primary gaze. In addition, she had right ear conductive hearing loss, leftward tongue deviation, and dysarthria characterized by slurred speech with pronounced variation in prosody. The motor examination was normal. The sensory examination revealed loss of pinprick, temperature sense, proprioception, and vibration distally in all extremities. She was areflexic throughout. Severe axial and appendicular ataxias were noted, and she was unable to stand or ambulate.

Questions for Consideration:

1. What is the localization of this presentation?
2. What is the differential diagnosis?
3. What initial investigations will help to narrow the differential?

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From the University of Washington, Seattle.

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Section 2

The patient presented with subacute progressive nonpositional vertigo, diplopia, gait impairment, and dysarthria. Her examination revealed multiple cranial neuropathies (including significant ophthalmoplegia and multidirectional nystagmus), ataxia, and diffuse areflexia. Altogether, the findings of multiple cranial neuropathies and subacute ataxia are concerning for diffuse brainstem and cerebellar processes. Her examination additionally demonstrated peripheral neuropathy. A new peripheral nervous system diagnosis was considered, but this finding was ultimately felt to be consistent with her known diabetes-related or postchemotherapeutic peripheral neuropathy.

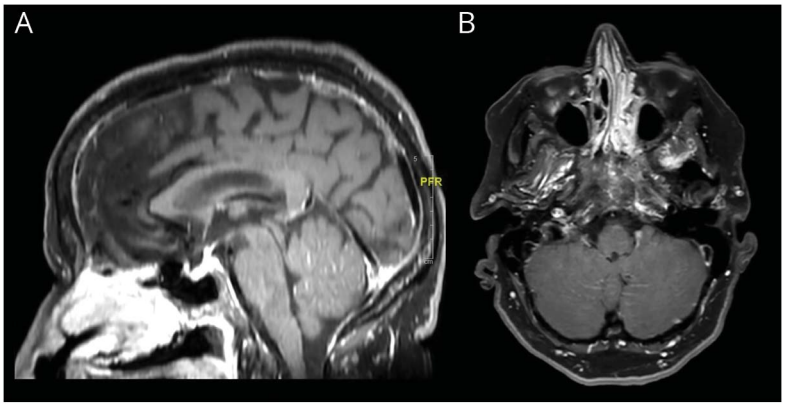
The differential diagnosis for this constellation of findings is broad, including but not limited to autoimmune/inflammatory processes, paraneoplastic disease, demyelinating disease, multifocal vascular disease, metabolic dysregulation/nutritional deficiencies, prion disease, infection, toxin exposure, and genetic diseases. Table 1 includes examples of etiologies initially considered, with the top considerations being a malignant or paraneoplastic process given her cancer history.

Initial investigations included brain MRI with and without gadolinium, MRA of the head/neck, and lumbar puncture. The brain MRI revealed mild diffuse volume loss, mild subcortical and periventricular white matter changes suggestive of chronic small vessel ischemic disease, and mild enhancement along the pial surface of the bilateral cerebellar hemispheres (Figure). The MRA was unremarkable. Our patient's CSF profile was notable for lymphocytic pleocytosis with a cell count of 91 cells/μL (88% lymphocytes, reference range 0–5), red blood cell count of 693 cells/μL (reference range 0–5), elevated protein of 179 mg/dL (reference range 15–45), and normal glucose of 70 mg/dL (reference range 40–80) with serum glucose 132 mg/dL. Flow cytometry and cytology on CSF samples were negative. The patient also completed a CT of the chest/abdomen/pelvis with contrast, which revealed enlarged right retrocrural and hilar lymph nodes along with ground glass opacities in the right upper lobe of her lung. Vitamin studies, including B12, E, and thiamine, and thyroid studies were within normal limits.

Questions for Consideration:

1. Do these results change your differential?
2. What additional investigations should you pursue?

Figure MRI of the Brain



Sagittal (A) and axial (B) T1-weighted images with gadolinium demonstrate mild enhancement along the pial surface of the bilateral cerebellar hemispheres.

Table 1 Relevant Differential Diagnoses Considered in the Presentation of Progressive Diplopia, Vertigo, and Ataxia

Category	Disease process
Paraneoplastic	Paraneoplastic cerebellar degeneration
Metastatic disease	Leptomeningeal carcinomatosis
	Brainstem metastases
Metabolic/nutritional	Wernicke encephalopathy
	Steroid-responsive encephalopathy associated with autoimmune thyroiditis
	Vitamin E and B12 deficiencies
	Celiac disease–associated ataxia
	Hypothyroidism
Autoimmune/inflammatory	Anti-GAD (glutamic acid decarboxylase) antibody-associated ataxia
	Sarcoidosis
	Behcet disease
	Systemic lupus erythematosus
Demyelinating	Multiple sclerosis
Vascular	Multiple posterior circulation infarcts
Infectious disease	Progressive multifocal leukoencephalopathy
	CNS Whipple disease
	Neurosyphilis
	Enterovirus/parechovirus
Toxins	Mercury poisoning
	Heroin pyrolysite
	Solvent inhalation (e.g., toluene)
Genetic diseases	Spinocerebellar ataxia (e.g., SCA 36, 37, and 38)
Prion disease	Creutzfeldt-Jakob disease

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Section 3

The findings of pial enhancement along the bilateral cerebellar hemispheres and lymphocytic pleocytosis and elevated protein on CSF studies raised most concern for an infectious cause, a paraneoplastic process, or metastatic disease. Indolent infections such as neurosyphilis, progressive multifocal encephalopathy (related to HIV infection or immunosuppression), CNS Whipple disease, and infectious encephalitides with predilection for the brainstem, such as enterovirus and parechovirus, are rare but were all considered. Given concern for a primary malignant process, specifically leptomeningeal carcinomatosis, repeat lumbar puncture was performed with additional flow cytometry and cytology showing no cancerous cells, although the negative predictive value of these studies is known to be low.[1] CSF infectious studies including VDRL, HIV, West Nile virus, enterovirus, and parechovirus were all negative. Additional testing revealed CSF-restricted oligoclonal bands, indicative of an intrathecal immunologic phenomenon. Serum autoimmune paraneoplastic panel returned positive for Purkinje cell cytoplasmic antibody type 1 (PCA-1-IgG or anti-Yo), with a titer of 1:61,440 consistent with a diagnosis of paraneoplastic cerebellar degeneration (PCD) with anti-Yo antibodies.

Questions for Consideration:

1. What treatment would you start?
2. What prognosis would you expect?

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Section 4

Given the initial concern for an unspecified autoimmune/inflammatory process with ophthalmoplegia, ataxia, and dysarthria, the patient was initially treated with IV immunoglobulin (IVIg) 2 g/kg given over 4 days. The patient had mild subjective improvement in her diplopia; on examination, there was some improvement but no resolution of the nystagmus and dysarthria. The rest of the neurologic examination including truncal and limb ataxia remained the same. Endobronchial ultrasound bronchoscopy with biopsy of pulmonary lymphadenopathy was performed to rule out another primary malignancy and showed only normal lymphoid tissue. Repeat cancer antigen 125 level (CA-125) was mildly elevated, but restaging of her ovarian carcinoma otherwise demonstrated no recurrence. To treat anti-Yo paraneoplastic syndrome, plans were made to continue with IVIg 1 g/kg every 3 weeks, and initiation of cyclophosphamide was considered. Unfortunately, the patient fell out of bed and developed a subdural hematoma. Given the change in her clinical status, the patient and family decided against pursuing further treatment.

Discussion

PCD is a common presentation of antibody-associated paraneoplastic neurologic syndromes, accounting for 36% of definite paraneoplastic cases in 1 study.[2] The criteria for a definite paraneoplastic neurologic syndrome are defined as a classical syndrome and cancer that develops within 5 years of neurologic symptom onset.[3] If a paraneoplastic antibody is detected, search for a primary neoplasm must be conducted.[3] The most common variant of PCD is associated with anti-Yo antibodies (or Purkinje cell cytoplasmic antibody type 1); it accounts for nearly 50% of cases.[4] The majority of cases have been reported in women with pelvic or breast tumors (like our patient with high-grade serous ovarian carcinoma).[4] A few cases associated with lung malignancy have been reported.[5] The typical presentation involves subacute development of cerebellar deficits with plateau of symptoms within 6 months.[4] Other autoantibodies that produce a similar PCD picture include anti-Hu (lung cancer), ant-Tr (Hodgkin lymphoma), anti-Ri (most commonly associated with gynecologic and breast cancers), and antimetabotropic glutamate receptor type 1 (Hodgkin lymphoma).[2]

In 1 large study of 55 patients with anti-Yo autoantibody-related PCD, neurologic symptoms preceded the diagnosis of malignancy by up to 15 months.[6] Most patients with known cancer had limited oncologic disease at the time of onset of neurologic symptoms.[6] Three of the 55 patients studied presented with neurologic symptoms coincident with recurrence of malignancy that had previously been thought to be in remission.[6] In addition to a pancerebellar syndrome with ataxia of the limbs and trunk, symptoms suggestive of brainstem involvement are often noted (similar to our patient with multiple cranial neuropathies), and commonly cognitive and psychiatric deficits follow.[6] Early in the disease course, MRI of the brain is typically normal, with late cerebellar atrophy occurring in some patients.[6] Rarely, cases of cerebellar edema and associated diffuse leptomeningeal enhancement have been reported, but we are not aware of any prior cases of isolated leptomeningeal enhancement, as seen in our patient.[7,8] CSF abnormalities primarily include elevated protein, lymphocytic pleocytosis (more common shortly after symptom onset), and the presence of CSF-restricted oligoclonal bands.[6]

With regard to pathogenesis, neurologic symptoms are the result of tumor-induced autoimmunity against cerebellar antigens.[9] An underlying immunologic reaction occurs with cerebellar degeneration–related protein 2 that is ectopically produced by tumor cells leading to loss of immune tolerance to this protein and synthesis of the autoantibody.[10] Research is ongoing regarding the relative importance of autoantibodies and cytotoxic T lymphocytes in the neuronal loss seen with this condition.[9]

There are no evidence-based treatment options for PCD.[11] However, steroids, IVIg, plasmapheresis, and a variety of immunotherapies have been used with varying degrees of success.[11] The Yo antigen is an intracellular onconeuronal antigen rather than a cell surface antigen, thus unlikely to be reached without a cytotoxic immunotherapy, such as cyclophosphamide.[12] No specific immunotherapy has been consistently shown to improve outcomes.[10] Survival from time of diagnosis has been reported to be a median of 13 months.[2] There has been evidence of better prognosis with breast cancer–related anti-Yo PCD than that associated with ovarian cancer.[8] The majority of patients in prior studies died of progressive neurologic disability, with age ≥60 years and higher Rankin Scale scores predicting worse outcomes.[2] PCD remains a difficult condition to promptly recognize and treat.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Appendix Authors

Name	Location	Contribution
Marissa Sakoda, MD	University of Washington, Seattle	Designed and conceptualized the study; analyzed the data; and drafted the manuscript for intellectual content
Kasra Sarhadi, MD, MPH	University of Washington, Seattle	Analyzed the data and drafted the manuscript for intellectual content
P. Anne Weisner, MD, PhD	University of Washington, Seattle	Analyzed the data and drafted the manuscript for intellectual content
Shannon Tierney, MD	University of Washington, Seattle	Analyzed the data and drafted the manuscript for intellectual content
Yujie Wang, MD	University of Washington, Seattle	Designed and conceptualized the study; interpreted the data; and revised the manuscript for intellectual content

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