Clinical Reasoning:

A 55-year-old man with weight loss, ataxia, and foot drop

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SECTION 1

A 55-year-old man with prior alcohol abuse and an 80 pack-year smoking history was referred for evaluation of a 3-month history of subacute-onset, progressively worsening imbalance without back pain. He began using a cane to ambulate after multiple falls. He also described recent right foot weakness, numbness in his feet and fingertips, and unintentional 25-pound weight loss over the past year. His medical history was significant for hypertension, gastroesophageal reflux disease, diverticulitis, and pelvic abscesses. A paternal grandfather had lung cancer. He reported a remote history of IV drug use. General examination revealed cachexia. Neurologic examination findings were complex. Gait examination revealed severe ataxia, a high steppage gait on the right, and a positive Romberg sign. The total ataxia score using the Scale for Assessment and Rating of Ataxia (higher scores indicate increased severity)¹ was 14/40, including gait, 5/8; stance, 4/6;

sitting, 1/4; speech disturbance, 0/4; finger chase, 0/4; nose-finger test, 0/4; fast alternating hand movements, 2/4; and heel-shin slide, 2/4. Nystagmus was not present. Strength testing revealed hip and knee flexion weakness bilaterally (grade 4/5) and severe (grade 2/5) weakness of right ankle dorsiflexion and eversion but preserved inversion strength. Reflexes were brisk in the upper extremities and normal in the lower extremities and plantar responses were flexor. Sensory testing revealed absent lower extremity vibration, absent joint position at the toes, and reduced pinprick in the feet without a sensory level. Initial laboratory testing revealed a hemoglobin of 9.3 g/dL (normal range 13.5–17.5).

Questions for consideration:

1. Where is the neurologic localization in this case? Is it peripheral, central, or both?
2. What is the differential diagnosis?

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SECTION 2

Some clues from the history and examination were helpful in correctly localizing the lesion. Inversion strength, typically involved in a sciatic neuropathy or L5 radiculopathy, was spared, suggesting a common peroneal neuropathy. The patient had his legs crossed during the clinic visit, suggesting that habitually doing so may predispose to a common peroneal neuropathy given his recent weight loss.

The remaining findings of sensory ataxia with mild lower extremity weakness localized to either peripheral nerve (e.g., sensory ganglionopathy/polyradiculopathy) or spinal cord (dorsal and lateral columns). Brisk upper extremity reflexes with discordant preservation of lower extremity reflexes in the setting of severe vibration sensory loss and pyramidal distribution weakness favored a spinal cord process.

The differential diagnosis included the following:

1. Paraneoplastic neuronopathy/myelopathy
2. Inflammatory/autoimmune etiologies (e.g., chronic inflammatory demyelinating polyneuropathy [CIDP], Sjögren syndrome, demyelinating disease)
3. Neoplastic disorders
4. Nutritional deficiencies (e.g., vitamin B₁₂)
5. Cervical spondylosis
6. Toxic/metabolic (e.g., pyridoxine excess, chemotherapeutic agents)
7. Infectious (e.g., syphilis, HIV, cytomegalovirus, Lyme disease)

Sensory ganglionopathy or polyradiculopathy was a diagnostic consideration, but nerve conduction studies and EMG revealed only a right common peroneal neuropathy with conduction block at the fibular head (figure, A). Chronic immune sensory polyradiculopathy

Figure Nerve conduction study, somatosensory evoked potentials, and MRI in our patient

(A) Short segmental stimulation ("inching") across the fibular head with stimulation of the peroneal nerve (recording over the right extensor digitorum brevis muscle) demonstrates a 77% drop in amplitude between the first waveform (4.4 mV, stimulating 26 mm below the fibular head) and last waveform (1.0 mV, stimulating 66 mm above the fibular head), consistent with conduction block. (B) The right median somatosensory evoked potential revealed prolongation of the cortical N20 latency (24 ms; normal 16.9–21.9), clavicle-to-cortical (N9–N20) interpeak latency (12.1 ms; normal 7.8–10.5), and cervical-to-cortical (N13–20) interpeak latency (9.2 ms; normal 4.7–6.6), with a normal clavicle-to-cervical (N9–N13) interpeak latency. These findings indicate impaired conduction in central proprioceptive pathways serving the right upper extremity. Waveforms (numbers reflect average latency in ms in normal individuals; the letter N [negative] refers to upward deflections as per standard neurophysiology nomenclature): N5 = elbow; N9 = clavicle; N13 = cervical region; N20 = primary somatosensory cortex. (C) MRI cervical spine axial T2-weighted images at the C2/3 interspace revealed hyperintense signal within both dorsal columns (white arrow). Abbreviation: o = onset.

(a variant of CIDP)² remained a possibility as slowing proximal to the dorsal root ganglion may only be detectable by somatosensory evoked potentials (SSEPs). However, CSF examination was normal, including cell count, protein, immunoglobulin G index, and oligoclonal bands. The patient did not complain of dry mouth or eyes and lacked antinuclear antibodies, making Sjögren syndrome unlikely.³ Other investigations for potential causes of a polyradiculopathy/ganglionopathy, including serum protein electrophoresis with immunofixation, fasting glucose and hemoglobin A1C, and Lyme, HIV, and syphilis serologies, were unremarkable.

A paraneoplastic process was considered at an outside facility due to the weight loss, long history of smoking, and potentially multifocal neurologic process. Antineuronal nuclear antibody type 1 (Anti-Hu) is associated with a sensory neuronopathy and underlying small-cell lung cancer in smokers.³ However, a serum paraneoplastic autoantibody evaluation, brain MRI, body PET-CT, prostate-specific antigen, and colonoscopy were all normal, and no suspicious skin lesions for melanoma were seen.⁴

SSEPs were undertaken and revealed impaired conduction in central proprioceptive pathways serving the right upper extremity (figure, B) and lower

extremity. MRI cervical and thoracic spine revealed no multiple sclerosis lesions, which favor the dorsal spinal cord, and no impingement dorsally to suggest cervical spondylosis, both of which cause sensory ataxia.³ However, subtle dorsal column T2 signal hyperintensity was present (figure, C).

Malabsorption and nutritional deficiencies are an additional consideration in patients with weight loss and neurologic complaints. Vitamin B₁₂ deficiency was suspected, as subacute combined degeneration could explain the clinical syndrome, electrophysiology abnormalities, and MRI pattern.³ However, serum B₁₂ was normal (573 pg/mL; normal range 211–946). For low-normal B₁₂ values (<400 pg/mL in our laboratory), testing for elevations in methylmalonic acid is also important as it is more sensitive for detecting cellular deficiency. The alcohol abuse history and potential for thiamine deficiency to cause polyneuropathy led to empiric thiamine treatment followed by serum testing, which was normal. Serum vitamin E and folate were normal. There was no history of excess pyridoxine intake or chemotherapy use to suggest a toxic/metabolic etiology.³

Question for consideration:

1. What investigation would you recommend next?

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SECTION 3

Serum copper and ceruloplasmin levels were obtained. The patient's serum copper was 0.27 $\mu\text{g/mL}$ (normal range 0.75–1.45) and ceruloplasmin was 9.8 mg/dL (normal range, 15–30). Copper deficiency myelopathy was diagnosed. Serum zinc was normal. Laboratory analysis demonstrated a ferritin

of 5 mcg/L (normal range 24–336), and peripheral blood smear revealed hypochromic microcytic erythrocytes.

Question for consideration:

1. What is the cause of the copper deficiency and unifying diagnosis?

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SECTION 4

Serum immunoglobulin A tissue transglutaminase antibodies were evaluated and found to be markedly elevated (>100 U/mL; normal range <4). Subsequent duodenal biopsies revealed total villous atrophy diagnostic of celiac sprue. In this case, celiac disease led to (1) duodenal malabsorption of copper resulting in copper deficiency myelopathy; (2) weight loss contributing to the common peroneal neuropathy in the setting of habitual leg crossing; and (3) probable combined iron and copper deficiency anemia (from duodenal malabsorption).

We prescribed 8 mg of oral copper daily for 1 week followed by a taper of 2 mg each week until a maintenance dose of 2 mg daily was reached. A gluten-free diet was recommended and iron was replaced IV. Serum copper normalized after 6 weeks, and treatment was maintained at 2 mg/day. Two months after diagnosis, improvements in energy level, numbness, and foot drop were noted (with discontinuation of leg crossing), but imbalance had yet to improve.

DISCUSSION This case underscores that while ataxia, anemia, and weight loss should prompt consideration of a paraneoplastic process, neurologic manifestations of malabsorption should also be considered. Second, we highlight the differential diagnosis of sensory ataxia. Third, our case demonstrates that ataxia in association with celiac disease may reflect copper deficiency rather than a primary immune-mediated gluten ataxia.

The most common neurologic manifestation of copper deficiency–associated myelopathy is sensory ataxia.⁵ SSEPs often demonstrate dorsal column conduction slowing, and MRI may reveal nonenhancing dorsal column T2 signal hyperintensities—both were evident in our patient.⁵ Copper may cause a hypochromic microcytic anemia sometimes accompanied by sideroblasts,⁵ although these were not seen in our case. The low ferritin suggested potentially combined iron and copper deficiency as the cause of anemia and malabsorption in the proximal duodenum (where both are absorbed) as the underlying etiology.

Copper has a role in maintaining the structure and function of the nervous system through the mitochondrial respiratory chain via cytochrome *c* oxidase–associated electron transport and oxidative phosphorylation.⁵ Dysfunction of this process is thought to cause dorsal column degeneration and the associated sensory ataxia. This is not surprising, as similar dorsal spinal cord imaging abnormalities are described with mitochondrial disorders including leukoencephalopathy with brainstem and spinal cord involvement and high lactate⁶ and rarely with Leber hereditary optic neuropathy.⁷ Dorsal column T2 signal hyperintensities have also been reported with a variety of sensory ganglionopathies (from dorsal root ganglia degeneration and associated loss of central

projections), other nutritional deficiencies (vitamin B₁₂ and E), infectious etiologies (syphilis [tabes dorsalis], HIV [vacuolar myelopathy], and human T-lymphotropic virus type 1 [tropical spastic paraparesis]), paraneoplastic myelopathies (often with gadolinium enhancement),⁴ hereditary causes (e.g., Friedreich ataxia), and toxic/metabolic causes (methotrexate, cytarabine, and heroin).

In addition to the proximal duodenum, copper is also absorbed in the stomach. The most common cause of acquired hypocupremia is gastric surgery for peptic ulcer disease or bariatric surgery, but it may occur with excessive zinc intake (usually from denture creams or supplements).⁵ Oral iron may worsen copper deficiency by competing for absorption; therefore, we recommended IV iron in our patient.⁵ Due to its ubiquitous distribution and low daily requirement, dietary deficiency is rare and typically occurs with malabsorption or iatrogenic causes (e.g., total parenteral nutrition deficient in copper).⁵

Celiac disease is an immune reaction in the small intestine in response to eating gluten.⁸ Gluten-associated ataxia is postulated to be immune-mediated as cerebellar T-cell infiltration and Purkinje cell loss may occur, but its exact pathogenesis remains uncertain.⁹ Our case and prior reports of copper deficiency–associated sensory ataxia¹⁰ suggest that it may account for a proportion of patients previously suspected to have an immune-mediated gluten-associated ataxia and should prompt the clinician to closely scrutinize spinal neuroimaging and to obtain SSEPs to evaluate preganglionic sensory pathways.¹⁰

NOTE ADDED IN PROOF

During the processing of this article, the patient died of an unrelated aneurysmal subarachnoid hemorrhage. An autopsy performed at our institution showed, in addition to his basilar tip aneurysm and subarachnoid hemorrhage, severe axonal degeneration of posterior columns with wallerian degeneration and neuropil vacuolation; the cerebellum showed no evidence of inflammation.

AUTHOR CONTRIBUTIONS

Eoin P. Flanagan: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, study supervision. Andrea N. Leep Hunderfund: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Neeraj Kumar: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, study supervision. Joseph Murray: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. Karl N. Krecke: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. Brian J. Katz: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, contribution of vital reagents/tools/patients. Sean J. Pittock: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, study supervision.

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