Clinical Reasoning:

A 28-year-old woman with lower extremity spasticity and microcytic anemia

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SECTION 1

A 28-year-old woman with a medical history of asthma, diabetes, and morbid obesity broke her right leg 3 years prior to presentation related to slipping on icy ground. She underwent surgical intervention for a tibial fracture, followed by a lengthy rehabilitation process. She never regained her previous walking ability and in fact felt that her balance was worsening. She stumbled frequently, tripping over small obstacles or uneven ground, and had 3 falls over 6 months prior to presentation. She had lost about 100 pounds after a gastric banding procedure done shortly before her accident. She denied weakness or clumsiness in upper extremities, headaches, vertigo, lightheadedness, or loss of consciousness. There was no history of fever, chills, autoimmune disorders, skin rash, joint pain or swellings, blood clots, or miscarriages. No relevant family history of neurologic disorders was present. On

examination, she was noted to have a right foot drop, increased tone and hyperreflexia in lower extremities with a positive Babinski sign, and several beats of ankle clonus bilaterally. Her gait was slightly wide-based and unsteady and she had difficulties with tandem gait. Higher cognitive functions, speech, oculomotor examination, strength in upper extremities and the left leg, and sensory examination including pinprick, light touch, temperature, vibration, and proprioception was normal. She had normal coordination in upper extremities and mild difficulties with heel to shin testing bilaterally related to spasticity.

Questions for consideration:

1. What is the localization of this patient's examination findings?
2. What differential diagnosis would you consider at this point?

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SECTION 2

Lower extremity spasticity and hyperreflexia with a pathologic Babinski sign and no sensory deficits is characteristic of upper motor neuron pathology. In the absence of abnormal findings in the upper extremities, low cervical or thoracic myelopathy affecting primarily motor pathways must be ruled out. Ataxic gait can be due to a sensory ataxia, which is ruled out by the absence of sensory deficits in our patient. The absence of appendicular ataxia or oculomotor or speech abnormalities makes a cerebellar pathology unlikely. A structural abnormality leading to compression of the spinal cord must be ruled out. Other important etiologies for myelopathies are autoimmune, nutritional deficiencies, infectious, and inflammatory.

Autoimmune and inflammatory disorders like multiple sclerosis, systemic lupus erythematosus, Sjögren syndrome, and celiac disease have to be considered. Metabolic and infectious causes of myelopathy include vitamin B₁₂, vitamin E, and copper deficiencies, HIV, and human T-cell lymphotropic virus infection. Of note, our patient had a history of gastric banding, which typically does not lead to nutritional deficiencies because it is a restrictive procedure, as opposed to malabsorptive procedures such as Roux-en-Y and gastrojejunol bypass surgeries. Finally, despite a lack of positive family history, a genetic condition such as

spinocerebellar ataxia or hereditary spastic paraplegia should be considered as well.

Laboratory studies revealed microcytic anemia with a hemoglobin level of 9.1 g/dL. The patient's thyroid panel, liver function tests, vitamins B₁₂ and E, serum copper, zinc, and ceruloplasmin levels were normal. Endomysial immunoglobulin A (IgA), tissue transglutaminase immunoglobulin A (IgG), and gliadin IgG and IgA antibodies were negative. An ELISA screening test for HIV antibodies was negative. Antinuclear antibody testing was positive with a titer of 1:320 and a homogeneous pattern, but double-stranded DNA antibodies, Sjögren antibodies, anti-Smith, and anti-RNP were negative. CSF examination revealed normal glucose and protein with absent cells, normal IgG synthesis rate, absent oligoclonal bands, negative Lyme antibodies, and normal angiotensin-converting enzyme levels. Electrophysiologic testing was consistent with a right peroneal neuropathy localizing above the short head of the biceps, thought to be related to an injury at time of surgery for her broken leg. MRI of the brain and cervical and thoracic spine with and without contrast did not reveal significant structural abnormalities.

Question for consideration:

1. What further testing would you consider to obtain a diagnosis?

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SECTION 3

In the absence of structural or metabolic abnormalities underlying her gait difficulties and spasticity, genetic testing for hereditary spastic paraplegia (HSP) was sent and revealed mutations in the *SPG11* (spatacsin) gene on both alleles, consistent with a diagnosis of HSP.

The patient was referred to a hematologist for evaluation of her anemia. Her positive antinuclear antibodies were not believed to be indicative of lupus and no treatment was initiated. Anemia was attributed to menorrhagia and she was started on iron supplements. Her

anemia did not improve with iron supplementation and further workup revealed blood in her stool. She was therefore referred to a gastroenterologist. She underwent a colonoscopy and was found to have a high-grade adenocarcinoma of the sigmoid with metastases to the liver. Treatment with neoadjuvant chemotherapy was initiated.

Questions for consideration:

1. Is there a relationship between HSP and cancer?
2. What treatment can be offered?

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SECTION 4

Colorectal cancer in our patient was probably not related to her HSP diagnosis. Interestingly, hypermethylation of the *SPG20* promoter has recently been found to be a biomarker for colorectal cancer. *SPG20* encodes for the spartin protein. Hypermethylation of the *SPG20* promoter region causes downregulation of spartin protein, which in turn results in cytokinesis arrest, a condition thought to be associated with carcinogenesis.¹

No curative treatment for HSP is available. Spasticity is often improved by muscle relaxants. Symptomatic treatment options include oral or intrathecal baclofen, tizanidine, and dantrolene. Botulinum toxin injections can be beneficial in some patients.² Supportive treatment with physical therapy is recommended and gait aids become necessary with progression of the disease. There also may be a role for gait phase-dependent transcutaneous peroneal nerve stimulation.^{2,3} Our patient benefitted from starting baclofen and undergoing physical therapy.

DISCUSSION HSP is a genetically and clinically heterogeneous group of disorders. There are more than 50 genetic types of HSP described to date, numbered in the order of discovery. Clinically, they are classified into complicated and uncomplicated forms. Uncomplicated forms present with progressive spasticity and variable degrees of weakness and some dorsal column impairment. In contrast, complicated forms have additional neurologic abnormalities such as cognitive impairment and ataxia.²

The most common clinical features are progressive lower extremity spasticity and variable weakness. Spasticity is greatest in hamstring, quadriceps, adductor, and gastrocnemius-soleus muscles.² Variable sensory loss is present. Progression of disease symptoms varies and may include a relative static course vs continuous progression or initial worsening with a stable plateau phase.

The major pathologic feature is degeneration of distal ends of the corticospinal tract and fasciculus gracilis.² At the molecular level, HSP proteins play important roles in removal of misfolded protein in mitochondria; axonal transport, synthesis, metabolism, and distribution of lipids; and DNA repair.⁴

SPG11 is the most common autosomal recessively inherited form of HSP, caused by a mutation in the spatacsin gene on chromosome 15q.^{5,6} Clinically, it is among the complicated forms of HSP characterized by peripheral neuropathy and various degrees of cognitive abnormalities. In our patient, the peroneal neuropathy was most likely secondary to nerve injury during surgery and not a feature of her HSP. MRI

of the spinal cord can show significant atrophy, especially in *SPG6* and *SPG8*,⁷ which are autosomal dominant forms of HSP. *SPG11* is often associated with a thin corpus callosum on MRI brain studies,⁸ which was not appreciated in our patient.

This case serves as a cautious reminder that there is not always a unifying diagnosis explaining a patient's abnormal findings (Occam razor), but that patients are allowed to have as many diseases as they please (Hickam dictum). Our patient was a young woman with no family history of colorectal cancer and no relevant neurologic family history, yet it was important to pursue both her anemia and her gait disorder with a broad differential diagnosis in mind to avoid missing a potentially life-threatening disease.

AUTHOR CONTRIBUTIONS

Chaitanya Bonda: first draft of the manuscript, design and conceptualization of the study, analysis and interpretation of data. Pankaj Sharma: preparation of initial manuscript draft. Kathrin LaFaver: design and conceptualization of the study, analysis and interpretation of data, critical revision of the manuscript.

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DISCLOSURE

C. Bonda and P. Sharma report no disclosures relevant to the manuscript. K. LaFaver served as a consultant for US World Meds. Go to Neurology.org for full disclosures.

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