Clinical Reasoning:
A 28-year-old man with progressive gait disturbance and encephalopathy

SECTION 1
A 28-year-old man with sickle cell disease presented with 7 months of difficulty walking. Initial examination 3 months prior to admission to our hospital was thought to be consistent with a polyneuropathy. He was areflexic, was unable to stand on toes or heels with decreased sensation on the left foot to light touch and vibration, had difficulty with heel to shin, and was unable to perform tandem gait. Laboratory tests revealed anemia (hemoglobin 7.2 g/dL) and elevated creatinine (1.49 g/dL). HIV, antinuclear antibodies, antineutrophil cytoplasmic antibodies, hepatitis serologies, rapid plasma reagin, thyroid-stimulating hormone, copper, SSA/B, and Lyme titers were unremarkable. B12 deficiency (B12 188 pg/mL) and a mildly elevated erythrocyte sedimentation rate (ESR) at 24 mm/hour were found. Initial MRI brain showed multiple foci of fluid-attenuated inversion recovery hyperintense lesions in the subcortical and periventricular white matter. Lesions did not restrict on diffusion-weighted imaging (DWI); however, a few lesions demonstrated enhancement with gadolinium. MRI of the spine was unremarkable. Lumbar puncture (LP) was remarkable for a CSF protein of 144 mg/dL, leukocytes 43/μL (92% lymphocytes), erythrocytes 2,400/μL, and glucose 41 mg/dL. There were no oligoclonal bands. The patient was treated with IM injections of B12, without improvement in his deficits.

Questions for consideration:
1. What is the differential diagnosis of progressive gait disorder?
2. How do the initial CSF results argue against the exclusive diagnosis of B12 deficiency?
SECTION 2
Gradual gait ataxia can result from either a peripheral or a central process. Peripheral nervous system processes that affect large fiber nerves include nutritional, inflammatory, or hereditary neuropathies. CNS pathologies include conditions that affect the dorsal columns and cerebellum, such as multiple infarctions, demyelination, or neoplasia. The patient’s examination localized to both a peripheral and cerebellar process. B_{12} deficiency could have explained the large fiber neuropathy on examination, and possibly his MRI; however, it was insufficient to explain his subsequent course and CSF results. It is thought that patients with sickle cell disease are more prone to B_{12} deficiency due to increased requirement or decreased absorption in the terminal ileum secondary to recurrent sickling crisis. The CSF pleocytosis was inconsistent with B_{12} deficiency. The MRI lesions were nonspecific. T2 hyperintensities can be observed in B_{12} deficiency, but demyelinating and vascular conditions should also be included in the differential. Some lesions were not in classic locations for demyelinating disease and could be consistent with old infarctions from sickle cell disease, or from an inflammatory process like vasculitis.

Three months after his initial evaluation, the patient was admitted for worsening fatigue. MRI brain had interval development of multiple new foci of T2 prolongation, many of which enhanced and restricted on DWI (figure 1). LP was remarkable for a protein of 134 mg/dL, leukocytes 6/μL, erythrocytes 608/μL, glucose 45 mg/dL, negative cytology, and negative Epstein-Barr virus, varicella-zoster virus (VZV), JC virus, and herpes simplex virus studies.

Question for consideration:
1. What is the differential of restricted diffusion on MRI brain?

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Figure 1 Axial brain MRI fluid-attenuated inversion recovery, T1-weighted gadolinium-enhanced, diffusion-weighted imaging, and apparent diffusion coefficient sequences

(A, B) Axial brain MRI fluid-attenuated inversion recovery (FLAIR) sequences with subcortical white matter T2 hyperintensities involving bilateral corona radiata and centrum semiovale. (C) T1-weighted gadolinium contrast-enhanced sequence with left frontal area of enhancement. (D, E) Diffusion-weighted imaging restriction of the cerebellar vermis with corresponding apparent diffusion coefficient sequence. (F) FLAIR sequence with T2 hyperintensity of the vermis.
SECTION 3

The differential of restricted diffusion on MRI brain includes infarction, status epilepticus, abscess, Creutzfeldt-Jakob disease (CJD), neoplasm/lymphoma, and rarely acute demyelination. Diffusion restriction increases the likelihood of a vascular process. Sickle cell disease can cause vaso-occlusive crisis and a multifocal vasculopathy with recurrent infarction. Clinical and laboratory data ruled out status epilepticus, abscess, and CJD. Despite these findings, the patient had dissemination in space and time of T2 lesions on his MRI scan and a working diagnosis was multiple sclerosis (MS). He was treated empirically with IV steroids; however, his mental status rapidly declined, and he was subsequently transferred to our hospital for further care.

On examination he was lethargic, but arousable to light touch. He was oriented to person and time, and had a very poor attention span. He was perseverative and able to follow simple midline commands, but not embedded commands. Speech was fluent. A dressing apraxia was observed. Cranial nerves were intact. His motor examination was nonfocal. Sensory examination was intact. He had left dysmetria and difficulty with heel to shin on the left. He was ataxic with a wide-based gait.

Admission laboratory studies were notable for anemia (7.9 g/dL), nephrotic range proteinuria (spot urine protein 696 mg/dL), creatinine of 1.45 mg/dL, and profound hypoalbuminemia (1.4 g/dL). LP was negative for oligoclonal bands and cytology. CSF protein remained mildly elevated at 73 mg/dL, without pleocytosis. MRI showed multiple nonenhancing subcortical T2 hyperintensities in the brain and cervical and thoracic spine (figure 2). Diffusion restriction was noted in the left cerebellum. Compared to initial imaging, 6 months prior, there was progression and evolution of the subcortical hyperintensities.

At this point, certain features of the presentation were atypical for demyelinating disease. First, the waxing and waning mental status was atypical for MS. Second, the diffusion restriction and evidence of infarction on MRI was not consistent with a demyelinating etiology. Finally, though the CSF parameters improved, the rapid worsening of encephalopathy during conventional treatment with IV steroids argues against the diagnosis.

Questions for consideration:
1. How could sickle cell disease explain the encephalopathy?
2. What further investigations would you consider?
SECTION 4
There was concern for vaso-occlusive crisis from sickle cell disease to explain the MRI and worsening encephalopathy. He was emergently treated with erythrocyte exchange transfusion. There was brief, unsustained improvement in his mental status. Brain MRI showed interval development of multiple new foci of restricted diffusion involving the cortex and subcortical white matter in both cerebral hemispheres. Conventional cerebral angiography showed multifocal irregular vasculopathy of the small intracranial arteries, thought to be consistent with sickle cell vasculopathy.

Questions for consideration:
1. What is the differential of a multifocal small vessel vasculopathy?
2. What diagnostic test is needed to arrive at a definitive diagnosis?
SECTION 5
Diseases diffusely involving the small arteries of the brain include primary CNS angitis, drug-induced vasculopathy, infectious (HIV, VZV, neuroborreliosis), neoplastic such as intravascular lymphoma, or autoimmune etiologies such as lupus cerebritis.

Due to the patient’s progressive multifocal cerebral lesions and unremitting encephalopathy, he underwent a brain biopsy of the right frontal lobe. Biopsy revealed intravascular large B-cell lymphoma. Lactate dehydrogenase (LDH) at the time of diagnosis was 1,098 U/L. PET scan revealed evidence of systemic lymphoma including bone, abdominal lymph nodes, adrenal, and brain involvement. The patient is currently undergoing rituxan, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (R-EPOCH) therapy. Ambulation and mental status have improved with chemotherapy.

DISCUSSION
Intravascular large B-cell lymphoma (IVLBCL) is a non-Hodgkin extranodal B-cell lymphoma in which growth is restricted to the lumina of the vessels. It is a rare disease occurring in fewer than 1 person per million, and primarily affects the middle-aged to elderly population. To our knowledge, this is the youngest reported patient with IVLBCL. By the time of presentation, most patients have advanced disease and often the diagnosis is made at autopsy.5 Even when the diagnosis is made premortem, the prognosis remains poor, with a mortality rate over 80%.4

IVLBCL is notorious for being the “great masquerader” as it usually presents with a myriad of nonspecific systemic and neurologic symptoms. Common manifestations are fever, skin rash, and encephalopathy.2 In retrospect, our patient developed a rash during his hospitalization, characterized by hyperpigmented macules located on his neck, and the skin may have been another potential site of tissue diagnosis. The most common laboratory findings reported are elevated LDH, anemia, elevated ESR, thrombocytopenia, and hypoalbuminemia. Nephrotic syndrome has also been documented.5 Our patient’s nephrotic syndrome was thought secondary to focal segmental glomerulosclerosis, the most common form of nephrotic syndrome in sickle cell disease, but biopsy was not pursued secondary to the patient’s encephalopathy.

Radiographically, ischemic brain lesions can be seen in about 50% of patients with IVLBCL. It is believed that massive proliferation of neoplastic cells causes vessel occlusion and cerebral infarcts.2 In a retrospective series of 5 patients, a dynamic pattern of MRI lesions with resolution and relapse of some DWI or T2 lesions was suggestive of the diagnosis of IVLBCL.6 The DWI sequences proved helpful in defining the patient’s pathology as likely infarction, though his antecedent sickle cell disease greatly complicated the differential diagnosis.

A rapid and aggressive clinical course with lack of response to conventional treatment should prompt further evaluation. In the course of his illness, this patient’s diagnoses ranged from a deficiency state to demyelination to infarctions associated with his known sickle cell disease, all subsequently proved incorrect. Two recent articles7,8 have described similar cases of patients with progressive neurologic symptoms and evolution and resolution of multifocal MRI lesions with IVLBCL. This case illustrates the difficulty in diagnosing IVLBCL when confounded by the comorbid diagnosis of sickle cell disease. A very high index of suspicion is important for the diagnosis of IVLBCL and tissue biopsy is mandatory for definitive diagnosis.

AUTHOR CONTRIBUTIONS
A.M. Massaro: primary author on this case, designed the teaching file, interpreted the data, drafted and revised the case. A. Pruitt: made substantial intellectual contribution to the teaching file, including conceptualization and multiple revisions.

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