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Clinical Reasoning: An unusual cause of transverse myelitis?

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SECTION 1

A 71-year-old woman presented with a 1-week history of progressive weakness involving her lower extremities, leading to an inability to walk. She also noticed diminished sensation in her lower extremities. She did not complain of bowel or bladder dysfunction. She did not have any neurologic symptoms in her upper extremities. She experienced an upper respiratory tract infection 5 days prior to the start of these symptoms and was treated with antibiotics. There was no history of headache, impaired cognition, or speech impairment.

Her examination revealed normal higher mental functions and intact cranial nerve function bilaterally. She had increased tone in both lower extremities, and

muscle strength was 3/5 at the hips and 2/5 at the knees and ankles. The weakness was in a pyramidal distribution with the flexors more affected than extensors. Sensory examination revealed diminished vibration and joint position sense up to her knees; a sensory level for fine touch and pinprick was detected at approximately the T6 level. She had exaggerated reflexes in her lower extremities with no clonus and had extensor plantar responses bilaterally.

Questions to consider:

1. What is the localization of the problem?
2. What are the likely etiologies?
3. What would you do next?

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SECTION 2

The involvement of multiple long tracts, increased tone, hyperreflexia, sensory level at T6, and no symptoms or signs in the upper extremities point to a lesion in the thoracic spinal cord.

The evolution of these complaints over a week would make a vascular etiology unlikely, and the differential for this patient includes demyelinating, inflammatory, infectious, neoplastic, compressive, and metabolic causes.¹ In a patient presenting with an acute onset of clinical features consistent with a myelopathy, an urgent MRI of the spine with contrast should be obtained to rule out

compressive causes that would require urgent surgical intervention.²

An MRI of the spine was obtained, which demonstrated a longitudinally extensive intramedullary spinal cord lesion extending from T6 to T12 (figure). Due to her compromised renal function, gadolinium contrast could not be administered. A diagnosis of transverse myelitis, possibly postinfectious, was made, and she was started on IV methylprednisolone 1 g daily for 5 days.

Question to consider:

1. Given the MRI findings, what would the differential diagnosis be?

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Figure Neuroimaging

(A) MRI sagittal short TI inversion recovery image of thoracic spinal cord demonstrates longitudinally extensive hyperintense signal extending from T6 to T12 spinal levels. (B) MRI brain axial T2 fluid-attenuated inversion recovery (FLAIR) image demonstrates multiple bilateral cortical and subcortical hyperintense lesions. (C) MRI brain axial T2 FLAIR image demonstrates bilateral cerebellar hyperintense lesions.

SECTION 3

Longitudinally extensive transverse myelitis (LETM) is a term used to describe confluent lesions extending more than 3 spinal cord segments. The differential diagnosis for LETM is fairly broad and a detailed list of causes is given in the table. LETM has gained recognition recently as being suspicious for neuromyelitis optica (NMO) and is part of the diagnostic criteria for this condition.³ Due to concern for this diagnosis, imaging of the brain was obtained.

MRI of the brain revealed multiple T2 hyperintense lesions bilaterally both infratentorially and supratentorially, as demonstrated in the figure, B and C.

Imaging features on spinal MRI can help refine the differential diagnosis of LETM. Multiple sclerosis (MS) cord lesions are usually peripheral, involve part of the cord, and have short longitudinal extent. NMO lesions are typically central, T1 hypointense, and cause cord expansion. Acute disseminated encephalomyelitis spinal cord lesions are similar to MS lesions, but MRI brain usually shows large confluent lesions with basal ganglia involvement. Spinal cord infarcts involve anterior cord with sparing of the dorsal columns, while dural arteriovenous fistulas usually show

T2 hyperintensity in the midthoracic cord with flow voids seen in the thecal sac.¹

The patient also underwent a lumbar puncture, which revealed leukocyte count 1 cell/mm³, erythrocyte count 2 cells/mm³, protein 47 mg/dL, glucose 57 mg/dL (serum glucose 104 mg/dL), immunoglobulin G index 0.6, negative cytology, and no oligoclonal bands. CSF varicella-zoster virus serology, herpes simplex virus PCR, Venereal Disease Research Laboratory, and Lyme serology were negative. Paraneoplastic panel, serum B₁₂, folate, thyroid-stimulating hormone, copper, zinc, anti-nuclear antibodies, rheumatoid factor, SS-A, SS-B, and NMO antibody were within normal limits.

The patient did not improve with IV steroids and continued to worsen in terms of her lower extremity strength and sensation. A course of plasma exchange was initiated for the possibility of a steroid-resistant demyelinating disease. Multiple studies have shown benefit from plasma exchange in fulminant CNS inflammatory demyelinating diseases.^{4,5} Nevertheless, over the next 2 weeks, she did not respond to plasma exchange and had no benefit from physical therapy.

Question to consider:

1. How would you further refine the diagnosis?

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Table Etiologies of longitudinally extensive transverse myelitis

Inflammatory	Noninflammatory
Autoimmune	Neoplastic
1. Neuromyelitis optica	1. Intramedullary metastases
2. Sjögren syndrome	2. Intramedullary tumor, such as ependymoma, intravascular lymphoma
3. Systemic lupus erythematosus	3. Paraneoplastic syndrome—CRMP5 antibody
4. Neurosarcoidosis	
5. Neuro-Behçet syndrome	
6. Multiple sclerosis	
7. Acute disseminated encephalomyelitis	
Infectious	Metabolic
1. Syphilis	1. Vitamin B ₁₂ deficiency
2. Tuberculosis	2. Copper deficiency
3. HIV	
4. Human T-lymphotropic virus type 1	
5. Schistosomiasis	
6. <i>Toxocara canis</i>	
Parainfectious	Vascular
1. Epstein-Barr virus	1. Spinal cord infarction
2. Cytomegalovirus	2. Spinal dural arteriovenous fistula
3. Herpes simplex virus	
4. Mycoplasma	
5. Varicella-zoster virus	
Radiation therapy-related	

SECTION 4

Repeat imaging showed some progression of the longitudinal extent of the spinal cord lesion and stable brain lesions. At this point, a brain biopsy was considered, given the lack of response to therapy directed at inflammatory and demyelinating disease.

Brain biopsy of a frontal lobe lesion was performed and revealed metastatic small-cell carcinoma. CT chest was then done and revealed a left hilar mass suggestive of a neoplasm. The hilar mass was not biopsied due to the positive brain biopsy and radiologic appearance of the mass. A diagnosis of longitudinally extensive spinal cord lesion secondary to intramedullary metastasis from stage IV small-cell lung cancer was made. She was seen by the oncology service and chemotherapy was initiated. However, she continued to worsen and was ultimately transferred to hospice.

DISCUSSION LETM has a broad differential diagnosis. However, the most common causes of LETM are inflammatory demyelinating diseases such as NMO and postinfectious encephalomyelitis. The presence of numerous brain lesions makes NMO less likely, though brain lesions may occur in patients with NMO, producing the so-called NMO spectrum disorder (NMOSD).⁶ NMOSD brain lesions are usually asymptomatic and may consist of periependymal lesions around the ventricular system, extensive hemispheric lesions, and lesions in the internal capsule and cerebral peduncles.⁷ NMO immunoglobulin G or aquaporin-4 antibody positivity was included in the diagnostic criteria for NMO in 2006 and improved recognition of the disease. It should be noted that the sensitivity of NMO IgG varies in different series from 51% to 90%, while its specificity lies between 91% and 100%.

Postinfectious encephalomyelitis can cause LETM and brain lesions, similar to those of our patient. A recent prospective study described the clinical features and course of postinfectious neurologic syndromes.⁸ These ranged from isolated encephalitis or myelitis to more diffuse encephalomyeloradiculoneuritis. Patients with postinfectious neurologic syndromes were older, had more severe neurologic disability at onset and poorer outcomes, and were more resistant to steroid treatment than patients with MS.⁸ In contrast to our patient, almost 90% of patients with postinfectious neurologic syndromes had elevated CSF counts suggesting inflammation, in addition to elevated CSF protein levels.

Intramedullary spinal cord metastases presenting as LETM are rarely encountered.⁹ Intramedullary spinal cord metastases are seen in only 0.1%–0.4% of cancer patients.¹⁰ In a recent retrospective review of intramedullary spinal cord metastases, they were the presenting feature in 20% of patients.¹¹ The underlying malignancy was lung cancer in 50%, followed by renal carcinoma, breast cancer, and melanoma.

Almost all intramedullary spinal cord metastases in this review exhibited enhancement with gadolinium and had extensive edema on T2-weighted sequences above and below the metastasis.¹¹ In our patient, the diagnosis might have been facilitated if gadolinium contrast had been administered, as this could have revealed an enhancing nodule within the longitudinally extensive spinal cord lesion.

Some of the clues pointing us away from an inflammatory cause in our patient were the patient's advanced age, lack of pleocytosis in the CSF, and lack of response to steroids and plasma exchange. It should also be noted that in our case the term "myelitis" is a misnomer, since there is no inflammatory lesion of the cord. This case highlights the importance of recognizing the broad differential diagnosis of LETM and appropriately utilizing invasive tests such as brain biopsy when patients do not have the expected response to therapy, especially when imaging and laboratory studies do not fully support the working diagnosis.

AUTHOR CONTRIBUTIONS

Dr. Bhargava conceptualized and drafted the manuscript. Dr. Elble critically revised the manuscript for important intellectual content.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

P. Bhargava reports no disclosures. R. Elble has received consulting fees from the Kinetics Foundation, and he receives research grant support from GlaxoSmithKline, Phytopharm, TEVA, the NIH (National Institute of Neurological Disorders and Stroke), and the Spastic Paralysis Research Foundation of Kiwanis International, Illinois-Eastern Iowa District. Go to Neurology.org for full disclosures.

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Neurology 2014;82:e46-e50

DOI 10.1212/WNL.0000000000000104

This information is current as of February 10, 2014

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