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Clinical Reasoning: A 64-year-old woman with progressive quadriparesis

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SECTION 1

A 64-year-old right-handed woman presented to an outside hospital with a 1-week history of weakness noted while walking. She reported bilateral weakness greater on the right, and several falls. She denied lower extremity numbness. Her medical history was significant for lower-back osteoarthritis and a 20 pack-year smoking history. She denied constitutional symptoms. Her examination on admission was notable for 4/5 right gastrocnemius strength and unsteady gait.

During hospitalization, her right-sided weakness progressed until she collapsed. She also noted hand weakness and intensified back pain, and required bladder catheterization because of difficulty urinating. Upon transfer to our hospital, the patient's vitals were stable and her examination was significant for mild ankle edema. Neurologic examination demonstrated 4/5 weakness in her arms bilaterally and 2/5 weakness in her legs bilaterally; sensory deficits were absent. Reflexes were diminished throughout and absent in the left leg.

Questions for consideration:

1. Where does this process localize?
2. With what syndrome does this patient present?
3. What is your first diagnostic step?

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SECTION 2

This patient presented with signs of a subacute progressive myelopathy. Quadriparesis and bladder dysfunction indicate a lesion at the level of the midcervical spinal cord affecting ventral/lateral spinal cord or spinal nerve roots. Without upper extremity involvement, the lesion would localize to the lower spinal cord or cauda equina. By contrast, a pattern of distal weakness with hyporeflexia and no sensory deficit is typical of a motor neuron disorder. It is crucial to distinguish myelopathy from Guillain-Barré syndrome. Although reflexes may be lost in both syndromes, myelopathy has a unique pattern of functional loss, urinary dysfunction, spasticity, and MRI findings.

A careful history and examination guide the type and location of diagnostic imaging, typically an MRI with gadolinium of the spinal region of interest. CT myelogram is an alternative modality. These may reveal compressive lesions that can be corrected by surgery. In the absence of a compressive structural lesion, an intrinsic cord lesion suggests transverse myelitis (TM), an inflammatory myelopathy. Acute inflammatory lesions may enhance with IV gadolinium. The causes of the myelitis should then be investigated with lumbar puncture and serologic studies. When considering multifocal processes such as demyelinating or metastatic lesions, a brain MRI with contrast should be performed.[1,2]

In this case, both CT and MRI were performed. Head CT was unremarkable. Brain MRI showed scattered T2 hyperintensities bilaterally. Spine MRI showed contrast enhancement in the cervical cord from C2 to C5 with lateral columns affected asymmetrically, right greater than left (figure, A and B). A chest CT, ordered based on incidental findings on spine CT, showed left lower lobe lung opacification and mediastinal lymphadenopathy (figure, C).

Questions for consideration:

1. What is the differential diagnosis for subacute TM?
2. What are the next steps in establishing a diagnosis for this patient?

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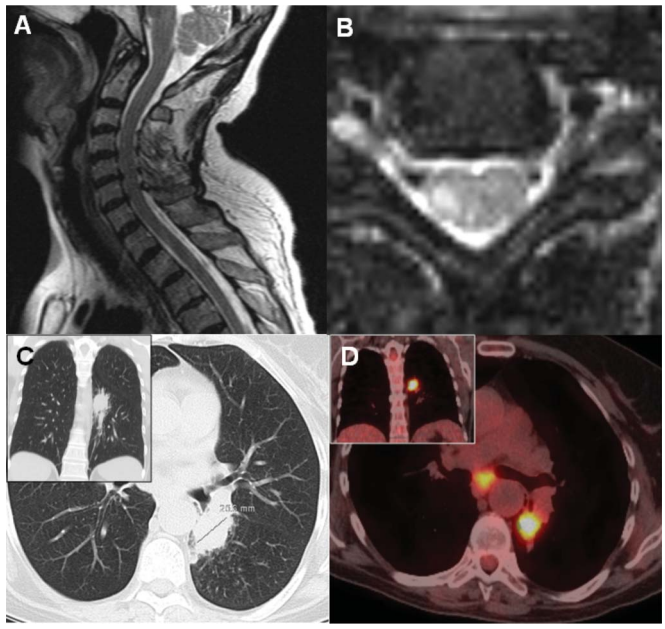
Figure MRI, CT, and PET results



(A) Magnetic resonance T2 sagittal turbo spin-echo (TSE) spine and (B) magnetic resonance TSE axial fat-saturated spine images show a cervical lesion from C2 to C5 with right-sided predominance of contrast enhancement. (C) Axial and coronal (inset) chest CT images show an enlarged left hilar pulmonary nodule. (D) Axial and coronal (inset) fluorodeoxyglucose-PET show increased metabolic state of a pulmonary nodule.

SECTION 3

Causes of myelopathy may be categorized as noninflammatory or inflammatory (table 1).[3] The most important immediate determination is to exclude a compressive cause, as rapid intervention may be necessary to preserve remaining cord function.

Complete vs partial transverse extent of the lesion suggests varying etiologies.[2–4] Longitudinal involvement over 3 vertebral levels suggests neuromyelitis optica (NMO) or other disease-associated TM, whereas enhancing lesions involving fewer than 2 cord segments are suggestive of multiple sclerosis (MS) or of idiopathic TM.[5] Concurrent brain MRI is useful as coexistent brain lesions suggest a diagnosis of MS in the presence of other diagnostic criteria.[3] Owl-eye or snake-eye pattern of hyperintensity suggests ischemic myelopathy, whereas nonenhancing myelopathy suggests B12 deficiency and amyotrophic lateral sclerosis. Neurosarcoidosis may produce leptomeningeal enhancement.

Given MRI findings consistent with spinal cord inflammation, lumbar puncture and serologic studies were performed (table 2). CSF pleocytosis, elevated CSF immunoglobulin G (IgG) index, and oligoclonal banding positivity indicated the presence of an inflammatory process. No autoimmune or paraneoplastic antibodies were detected. Investigation for infectious etiologies showed normal glucose measurement and negative PCRs (viral and Lyme), antibody-based detection (West Nile virus, cryptococcus), and culture (tuberculosis and fungi).

Based on the diagnosis of TM of noninfectious etiology, the patient was started on IV methylprednisolone. Plasmapheresis was also performed. However, she showed no improvement in symptoms.

Bronchoscopy was performed to investigate the pulmonary nodule seen on chest CT. The biopsy result was inconclusive. PET scan confirmed fluorodeoxyglucose-avid uptake in infrahilar soft tissue and mediastinal lymphadenopathy (figure, D), suggestive of hypermetabolism. A wedge resection of the lower left lobe lung nodule was consistent with small cell lung carcinoma with immunostaining positive for KI-67, CD56, AE1, and AE3, weakly positive for BER-EP54 and chromogranin, and negative for neuron-specific enolase.

Question for consideration:

1. What is the most likely etiology of the myelitis?

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Table 1 Etiologies of myelopathy

Noninflammatory		Inflammatory	
Trauma	Disk herniation	**Demyelinating**	MS, neuromyelitis optica, ADEM
Toxic/metabolic	Vitamin B12 deficiency	**Autoimmune**	Systemic lupus erythematosus, Sjögren syndrome, mixed connective tissue disease
Neurodegenerative	Spinocerebellar ataxia	**Paraneoplastic**	Anti-CRMP5
Neoplastic	Primary: glioma, ependymoma, lymphoma	**Bacterial**	Lyme disease, syphilis, tuberculosis, mycoplasma
	Secondary: metastases	**Viral**	Cytomegalovirus, HSV, VZV, hepatitis C, HIV
Vascular	Arteriovenous malformation or fistula, hemangioblastoma, cavernoma	**Fungal**	*Coccidioides immitis*
Other	Syringomyelia	**Parasitic**	Neurocysticercosis

Abbreviations: ADEM = acute disseminated encephalomyelitis; HSV = herpes simplex virus; MS = multiple sclerosis; VZV = varicella-zoster virus.

Table 2 CSF and serum studies results

Positive CSF studies	Lymphocytic pleocytosis, WBC 103 (tube 1; 94% lymphocytes, 2 RBCs) and 89 (tube 3)
	Total protein 118
	Positive oligoclonal bands (>5 well-defined γ restriction bands)
	IgG index IgG LOC 2.95 (<0.1)
	IgG, 20.3 (0.5–6.1)
Negative CSF studies	General: glucose 58; albumin 8.7 (normal <35)
	Microbiology: no microbial growth after 4 d; no acid-fast bacilli and fungi (after 14 d); cryptococcus antigen; acid-fast CSF direct smear; *Borrelia burgdorferi* DNA; West Nile RNA PCR
Positive serum studies	Antinuclear antibody 1:80, speckled pattern
	Anti-cardiolipin IgM 11 (normal <10)
	IgG index 0.86 (normal <0.7)
	IgG synthesis 46.2 (normal <3.3)
	Albumin index 22.8 (normal <9)
	IgG total index 1,037 (normal 694–1,618)
Negative serum studies	Nutritional: methylmalonic acid 0.17 (normal <0.4); B12 509 (normal); RBC folate 430 (normal 280–790)
	Coagulation: INR 1.0; PTT 29.1; C3 146 (normal 90–180); C4 28 (normal 16–47)
	Microbiology: RPR screen nonreactive; West Nile IgG and IgM; enteral virus DNA PCR; HIV-1 and -2; Lyme (IgG and IgM)
	Autoimmune/connective tissue: ESR 28; ACE 57 (normal 15–60); cardiolipin IgA <13; cardiolipin IgG <11; anti-dsDNA <1:10 (normal); thyroproteins not detected
	Metabolic: free T4 1.89; TSH 1.08 (normal 0.5–5)
	Paraneoplastic: NMO-IgG; neuronal nuclear anti-Hu; anti-Yo; anti-Ri; AChR binding antibody 0 (normal <0.02); striational antibody; N-type calcium-channel antibody 0 (normal <0.03); P/Q-type calcium-channel antibody 0 (normal <0.02); CRMP-5 IgG; ANNA-1; ANNA-2; ANNA-3; PCA-1; PCA-2; PCA-TR; amphiphysin antibody; AChR ganglionic 0 (normal <0.02); AGNA-1; neuronal voltage-gated K^+ 0 (normal <0.02)

Abbreviations: ACE = angiotensin-converting enzyme; AChR = acetylcholine receptor; AGNA = anti-glial nuclear antibody; ANNA = anti-neuronal nuclear antibody-1; CRMP = collapsing response-mediator protein; dsDNA = double-stranded DNA; ESR = erythrocyte sedimentation rate; Ig = immunoglobulin; INR = international normalized ratio; NMO = neuromyelitis optica; PCA = purkinje cell antibody; PCR = polymerase chain reaction; PTT = partial thromboplastin time; RBC = red blood cell; RPR = rapid plasma reagin; TSH = thyroid stimulating hormone; WBC = white blood cell.

SECTION 4

Small cell lung cancer (SCLC) likely resulted in a paraneoplastic syndrome causing subacute TM. The lack of a detectable paraneoplastic autoantibody does not exclude the diagnosis because undiscovered or untestable autoantibodies likely exist.[6,7] The chest CT was essential to identification of the SCLC and fluorodeoxyglucose-avid pulmonary nodule (figure, D). Neurologic examination by this time showed waxing and waning mental status and near complete paraparesis with 0/5 strength in lower extremities and 2–3/5 in upper extremities. Chemotherapy (cisplatin and etoposide) was initiated for SCLC along with IV immunoglobulin for TM. Her neurologic decline stabilized, and the patient was discharged to home for comfort care.

DISCUSSION TM is a heterogeneous group of acute and subacute inflammatory disorders with motor, sensory, and autonomic spinal cord dysfunction.[1] Multiple vertebral segments are involved; the lesion is not necessarily radiologically or pathologically transverse.[2] The annual incidence of TM is 1.3 to 8 cases per million.[1] Of patients diagnosed with TM, one-third recover completely, one-third have moderate residual disability, and one-third have severe residual disability.[3] The International Transverse Myelitis Consortium Working Group set 5 diagnostic inclusion criteria: 1) bilateral dysfunction; 2) sensory level; 3) progression to nadir between 4 hours and 21 days after onset; 4) demonstration of spinal cord inflammation; and 5) exclusion of noninflammatory causes. The pathologic findings are collections of lymphocytes and monocytes, demyelination, axonal injury, and microglial activation.[2]

Paraneoplastic myelopathy is a cancer-associated inflammatory dysfunction of the spinal cord. Paraneoplastic causes of TM may result in isolated tract involvement as in our patient with isolated motor involvement, rather than the typical combined motor and sensory findings in other etiologies. Risk factors for cancer should increase suspicion for paraneoplastic syndrome.[8] Paraneoplastic myelopathy is frequently associated with lung and breast cancer.[9] Spine MRI with contrast often reveals symmetrical hyperintense T2 lesions confined to individual tracts. Paraneoplastic disorders may have multifocal involvement.[8] In a recent case series, 65% of cases showed T2 abnormalities; 70% showed longitudinal extent of lesion exceeding 3 vertebral segments.[6] Although antibodies are not required for the diagnosis of paraneoplastic myelopathy, antibodies that are frequently associated are ANNA-1 (anti-Hu; 11%–60%), anti-amphiphysin (24%), ANNA-2 (anti-Ri; 18%), ANNA-3 (18%), anti-CRMP5 (16%), PCA-2 (10%), PCA-1 (anti-Yo; 5%), anti-Ma (4%), and anti-Ta (3%).[6] NMO-IgG antibody (targeting aquaporin-4) is specific to NMO, but may also be positive with MS, autoimmune disorders, and paraneoplastic myelopathy.[3]

In a recent report of 31 patients with paraneoplastic myelopathy (median age 62 years), 52% presented with a subacute progressive course.[6] CSF studies showed 77% had lymphocytic pleocytosis and 92% had elevated CSF protein; an autoantibody was detected in 81% of patients. Paraneoplastic myelitis frequently preceded the determination of a primary cancer (67%); identification of specific paraneoplastic antibodies may assist with this diagnosis (39%). Frequently affected areas of the spinal cord include the lateral column (25%), dorsal column (20%), and central gray matter (20%).[6] Our patient fit the profile of such a patient given her age, CSF findings, and imaging findings; furthermore, SCLC was found only after diagnosis of paraneoplastic myelitis in this patient.

The management of paraneoplastic myelopathy is similar to the management of other inflammatory causes of TM. High-dose IV corticosteroids are standard first-line therapy, with IV immunoglobulin as an alternative. Randomized controlled trials to guide treatment are lacking.[2] Adverse effects of corticosteroids include gastrointestinal symptoms, insomnia, headache, anxiety, mania, hypertension, hyperglycemia, and electrolyte disturbances. Plasma exchange is recommended in steroid nonresponders. One retrospective analysis showed plasma exchange displayed therapeutic benefit beyond steroids in TM patients without complete loss of motor and sensory function.[10] Complications of plasma exchange include hypotension, electrolyte imbalance, coagulopathy, catheter-related thrombosis, and infection. T-cell-depleting immunotherapies such as cyclophosphamide, tacrolimus, azathioprine, and mycophenolate have been reported to show benefit in paraneoplastic myelopathy.[6,9] B-cell-depleting immunotherapy such as rituximab may also be considered.[9]

The prognosis of TM varies by cause; in general, there is a 50% to 70% likelihood of attaining partial or complete recovery.[1] The disability of paraneoplastic myelopathy develops rapidly and is often permanent. Patients treated with chemotherapy or immunotherapy in one series rarely showed sustained improvement, with a significant association between younger age and clinical improvement.[6] Patients showed a 50% chance of being wheelchair-bound at 16 months with treatment and at 9 months without treatment.[6]

In summary, we have described a case of a myelopathy likely associated with an autoimmune response triggered by lung cancer. Paraneoplastic myelopathies are distinct in that they do not require sensory involvement, as in our case. Consideration of paraneoplastic myelopathy in the differential diagnosis will facilitate early recognition of this clinical phenomenon and guide appropriate treatment.

AUTHOR CONTRIBUTIONS

A. Gummadavelli: responsible for conceiving case report, manuscript preparation, generation of figure, manuscript revision, and approval. J.E. Motelow and N.S. Narayanan: responsible for conceiving case report, manuscript preparation, revision, and approval.

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DISCLOSURE

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