Challenging Myelopathy Cases

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Abstract

Misdiagnosis of myelopathies is common and can lead to irreversible disability when diagnosis- and disease-specific treatments are delayed. Therefore, quickly determining the etiology of myelopathy is crucial. Clinical evaluation and MRI spine are paramount in establishing the correct diagnosis and subsequently an appropriate treatment plan. Herein, we review an approach to myelopathy diagnosis focused on the time course of neurologic symptom progression and neuroimaging pearls, and apply them to a variety of inflammatory, structural, and vascular myelopathy cases.

Keywords

- myelitis
- spondylosis
- spinal cord infarction
- dural arteriovenous fistula

Determining the cause of myelopathy is crucial, as disability can accrue quickly and be substantial.[1] It is particularly important to identify treatable etiologies expeditiously, as failure to identify and treat the cause quickly can lead to permanent irreversible disability.

Misdiagnosis of myelopathies is common and many patients with hyperacute or progressive myelopathies are incorrectly labeled as having "transverse myelitis," which can lead to iatrogenic morbidity from inappropriate investigations or treatments.[2,3] To help narrow down the differential diagnosis, it is most important to consider the time from symptom onset to maximal neurologic deficit.[2–4] This time to nadir can be categorized as hyperacute (<12 hours), acute/subacute (1–21 days), or chronic/progressive (progression beyond 21 days).[4] Hyperacute presentations may suggest a vascular etiology such as spinal cord infarction (SCI),[5] whereas acute/subacute myelopathies are often inflammatory or infectious,[4,6] and chronic/progressive presentations warrant consideration of alternative causes including those that are structural (e.g., cervical spondylosis), vascular (e.g., spinal dural arteriovenous fistula), inflammatory/demyelinating (e.g., primary progressive multiple sclerosis [MS]), other inflammatory (e.g., sarcoid), nutritional (e.g., copper or vitamin B12 deficiency), neoplastic (e.g., astrocytoma), hereditary (e.g., hereditary spastic paraparesis), or degenerative (e.g., amyotrophic/progressive lateral sclerosis).[4,7–10] In this article, we will apply this approach with clinical and radiological clues to discuss a variety of myelopathy presentations while highlighting diagnostic strategies, treatment approaches, and areas of uncertainty.

Case Presentation 1

A 39-year-old man with a background history of hypertension and hyperlipidemia presented to the emergency department with severe acute weakness in his upper extremities. The prior evening, the patient noticed several episodes of brief "wrapping" sensations around his chest that resolved spontaneously within seconds. These sensations were quite unpleasant and worrisome. After the fifth sensation of wrapping around his chest, he had a persistent feeling of vague numbness in his bilateral hands. He decided to go to bed early as he was worried he might be getting sick.

He awoke 7 hours later with near-complete plegia in his hands and wrists bilaterally and noticed mild sensory loss in this region as well. As he was getting out of bed, he also noticed weakness in his proximal upper extremities. Additionally, he felt severe discomfort over his left shoulder, cramping in his right arm, and noticed that his right-sided chest muscles were twitching. There were no symptoms in his lower extremities.

He was immediately brought to our emergency department where he was found to be hypertensive to 173/101 mm Hg on arrival. Neurological examination at that time revealed

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flaccid weakness in the upper extremities most severely affecting the left triceps and distal wrist and hand muscles bilaterally. He was areflexic throughout, and there were no significant sensory changes. Strength testing in the lower extremities was normal.

Clinical Problem (Localization)

This patient's presentation of acute flaccid weakness in the upper extremities with areflexia and sparing of lower extremity symptoms is unusual. An acute myelopathy localized to the cervical spinal cord is possible, particularly one involving the anterior horn cells predominantly.

Strategies for Evaluation

Diagnostic Reasoning

Given the acute or moreover hyperacute (<12 hours) onset of symptoms, particularly with rapid onset of severe flaccid weakness with associated pain, a vascular etiology of myelopathy such as SCI should be at the top of the differential diagnosis.

Management Recommendations

An emergent magnetic resonance image (MRI) of the cervical spine was performed (►**Fig. 1**) and showed a pencil-like T2-hyperintense signal extending from C4 to C6, in a pattern predominantly involving the ventral horns. There was no evidence of compression. These findings, in addition to the clinical history, were highly suggestive of spontaneous SCI as the likely diagnosis. He was given phenylephrine to augment his mean arterial blood pressure (MAP) and a lumbar drain was placed emergently by neurosurgery to facilitate increased spinal cord perfusion.

A thorough diagnostic workup to rule out alternative etiologies of acute myelopathy was undertaken and revealed normal serum studies including aquaporin-4 (AQP4)-IgG, myelin oligodendrocyte glycoprotein (MOG)-IgG, vitamin B12, syphilis serology, anti-SSA, and anti-SSB. Cerebrospinal fluid (CSF) analysis revealed a normal white blood cell count of 1 cell/mm^3 (reference range, 0–5), protein of 37 mg/dL (reference range, 15–45 mg/dL), glucose of 77 mg/dL, and negative oligoclonal bands. MR angiography of the neck with T1-fat saturation showed no evidence of dissection and there was no herniated disc near the site of infarction to clearly suggest fibrocartilaginous infarction. Additional laboratory studies evaluating causes of hypercoagulability including protein C, protein S, dilute Russell's viper venom time screen, prothrombin gene mutation, fasting lipid panel, hemoglobin A1c, anti–double-stranded DNA, beta-2 glycoprotein antibodies, and antiphospholipid antibodies were normal.

Prognosis

Over the following days, the patient experienced dramatic improvement in strength with only severe left thumb weakness and mild weakness in the other left hand muscles remaining. He was initiated on aspirin 81 mg and atorvastatin 80 mg daily in addition to a 90-day course of clopidogrel 75 mg daily to aggressively try to prevent any further chance of thrombosis.

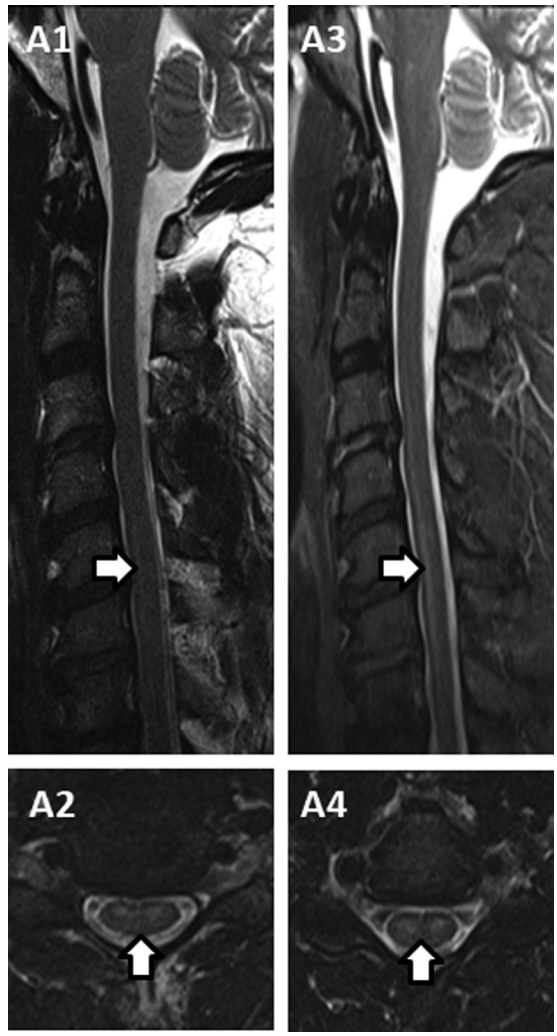

Fig. 1 MRI features of spinal cord infarction. Sagittal T2-weighted imaging of cervical spinal cord appeared essentially normal other than perhaps very faint possible signal around C4–C6 region (**A1**, arrow). STIR imaging sequences revealed bright focal signal in this region, which has a long anterior signal consistent with pencil-like T2-hyperintensity (**A3**, arrow). This was corroborated on axial T2-weighted imaging showing ventral horn patchy T2-hyperintensity at multiple levels (**A2, A4**: arrows).

Applicable Guidelines and Areas of Uncertainty

Spinal cord infarction is an underrecognized cause of acute myelopathy.[2,5] SCI can occur at any age, and often is associated with traditional vascular risk factors (e.g., high cholesterol, elevated blood pressure, diabetes, history of cardiovascular disease). However, a high number of SCIs are also caused by arterial dissection (aortic, cervical) and fibrocartilaginous embolism.[5]

In general, when a patient presents with a severe rapid-onset myelopathy, a SCI should strongly be considered, particularly when severe deficits accumulate within 12 hours of

symptom onset. The presence of acute severe pain is also helpful in diagnosing SCI, as this is rare in the presentation of an inflammatory myelopathy.[5] An emergent MRI will help differentiate the myelopathy etiology, especially if acutely the MRI is normal, yet severe myelopathy deficits remain, which is typical for SCI. Other classic neuroimaging findings such as anterior horn cell T2-hyperintensity in an "owl eyes" pattern, and anterior "pencil-like" signal are common in SCI; however, imaging findings may be quite diverse. Also, diffusion restriction is helpful at making the diagnosis when present, but sensitivity is only about 70% and should not exclude the diagnosis when absent.[5]

Other categories of acute myelopathy that should be considered in this setting include spinal cord compression (e.g., disc, tumor, blood, infection), hemorrhage, vascular malformation (e.g., arteriovenous malformation), severe inflammatory disease (e.g., NMOSD), toxic etiologies (e.g., heroin, nitrous oxide abuse), and rare infectious causes (e.g., syphilis vasculitis). When acute SCI is suspected, physicians should consider using IV recombinant tissue plasminogen activator if within the typical window for an acute ischemic stroke, or a lumbar drain with MAP augmentation to increase spinal cord perfusion.[11] The mechanism of SCI should always be sought, even though this is not often clear after evaluation, and vascular risk factors should be treated.

Conclusions and Recommendations

Hyperacute presentations of myelopathy, particularly with flaccid weakness and associated pain, should raise clinical suspicion for spontaneous SCI. Emergent spine imaging with MRI can reveal helpful clues including diffusion restriction in the acute setting and pencil-like or anterior horn cell predominant patterns of T2-hyperintense signal in the acute to subacute setting. Once spinal cord ischemia is strongly suspected, treatment should be initiated to increase spinal cord perfusion by MAP augmentation and lowering of pressure within the spinal canal via CSF drainage. Thereafter, a thorough investigation into potential mechanisms of SCI and vascular risk factor optimization should be undertaken.

Take-Home Points

- Hyperacute presentations (<12 hours) of severe myelopathy should bring vascular myelopathy etiologies such as spontaneous SCI to the top of the differential diagnosis.
- While vascular risk factors are commonly associated with spontaneous spinal cord infarction, other mechanisms such as arterial dissection or fibrocartilaginous embolism may be responsible and highlight that SCI can occur at any age.
- Treatment for SCI is directed to increase spinal cord perfusion by MAP augmentation and lowering of pressure within the spinal canal via CSF drainage.

Case Presentation 2

A 60-year-old woman presented with dizziness, back pain, and an unsteady gait. One week prior she had mild upper respiratory symptoms including rhinorrhea, cough, and a sore throat, all of which resolved spontaneously. Over the subsequent days, her sensation of dizziness worsened, and she developed ascending numbness and progressive weakness in her lower extremities to the point that she required a gait aid for ambulation, and urinary retention requiring catheterization. Neurologic examination at that time was notable for a moderate to severe flaccid paraparesis, with bilateral flexor plantar responses, and subjective numbness from the patient's knees to her toes.

Clinical Problem (Localization)

This patient's presentation is most suggestive of a subacute myelopathy, with progressive paraparesis, ascending symmetric sensory loss, and urinary retention serving as characteristic features. In this clinical scenario, the constellation of symptoms would localize particularly to the thoracic spine, perhaps with conus medullaris involvement given the flaccid nature to the myelopathy and the autonomic dysfunction. Furthermore, the patient's sensation of worsening dizziness may warrant consideration of an infratentorial process as well.

Strategies for Evaluation

Diagnostic Reasoning

To help narrow down the differential diagnosis, it is important to characterize the time from symptom onset to maximal neurologic deficit. In this patient, the subacute onset of symptoms with neurologic nadir between 1 and 21 days is suggestive of a myelitis, with inflammatory or infectious considerations at the top of the differential diagnosis.

Management Recommendations

MRI with and without gadolinium is the imaging modality of choice in the evaluation of subacute myelopathies. MRI of the spine in this particular case revealed a longitudinally extensive transverse myelitis (LETM; parenchymal T2 hyperintensity extending three or more vertebral segments) within the thoracic spine, predominantly affecting the gray matter in a pattern suggestive of an H sign, with a nonspecific enhancement pattern (►**Fig. 2A1–A4**). With a LETM detected, it is standard to also obtain an MRI of the brain as characteristic lesions, and if detected, can help in determining the underlying diagnosis. In this patient, MRI of the brain revealed a T2 hyperintense lesion with associated enhancement near the 4th ventricle and right middle cerebellar peduncle (►**Fig. 2B1–B2**).

Laboratory studies, particularly with serum (e.g., AQP4-IgG and MOG-IgG) and CSF biomarkers, provide powerful clues to aid in the diagnosis of myelitis as well. In this case, CSF analysis revealed a mild pleocytosis with a white blood cell count of 12 cells/mm^3 (reference range, 0–5), an elevated protein of 70 mg/dL (reference range, 15–45 mg/dL), normal glucose, and negative oligoclonal bands. Serum AQP4-IgG was negative; however, serum MOG-IgG was positive at high titer of 1:1,000 (normal <1:20). She was diagnosed with MOG-IgG-associated disease (MOGAD) and treated with IV methylprednisolone 1 g daily for 5 days. She had substantial

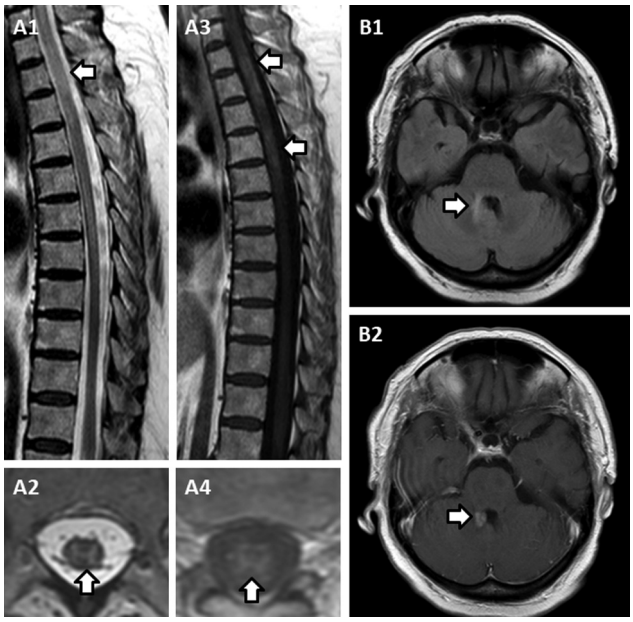

Fig. 2 MRI features of myelin oligodendrocyte glycoprotein IgG-associated disease. Sagittal T2-weighted thoracic spine MRI showing a longitudinally extensive T2-hyperintense lesion (**A1**, arrow), predominantly affecting the gray matter in a pattern suggestive of an "H sign" on axial T2-weighted sequences (**A2**, arrow). Sagittal (**A3**) and axial (**A4**) T1-weighted post gadolinium sequences show a nonspecific enhancement pattern (arrows). MRI of the brain shows a T2 hyperintense lesion near the 4th ventricle and right superior cerebellar peduncle on T2 FLAIR-weighted sequences (**B1**, arrow) with associated enhancement on T1-weighted post gadolinium sequences (**B2**, arrow).

recovery over the following months, with only mild residual bladder dysfunction and a mild sensation of burning in her lower extremities remaining. Empiric long-term immunosuppressant treatment was deferred in place of a watchful waiting approach.

Prognosis

The patient's excellent recovery with acute treatment is typical in MOGAD, which often responds better to treatment than AQP4-IgG-seropositive neuromyelitis optica spectrum disorder (AQP4-IgG-NMOSD). Empiric immunosuppressive treatment for attack prevention is typically used in cases that relapse. Often a watchful waiting approach is pursued at initial presentation as a monophasic course is commonly encountered.[12–15]

Applicable Guidelines and Areas of Uncertainty

Cell-based assay techniques have allowed for discovery of a spectrum of CNS demyelinating disease in MOGAD including monophasic/recurrent optic neuritis, acute disseminated encephalomyelitis, monophasic/recurrent myelitis, and AQP4-IgG seronegative NMOSD or combinations thereof. Compared with AQP4-IgG-NMOSD, MOGAD typically has a milder phenotype and a more robust response to treatment.

While imaging features in MOGAD may overlap with AQP4-IgG-NMOSD, with both often having an LETM, T2-hyperintense spinal cord lesions in MOGAD may be discontinuous, frequently are gray-matter predominant on axial images, will often involve the conus, and have only subtle or absent associated gadolinium enhancement. In contrast, AQP4-IgG-NMOSD usually has a solitary longitudinally extensive T2 hyperintensity, frequently with cord swelling, and more robust enhancement at times in a ringlike pattern.[16,17] Lesions diffusely involving the middle cerebellar peduncle favor MOGAD over AQP4-IgG-NMOSD, which more often affects the area postrema, and MS, in which short peripheral lesions are more common.[18]

Laboratory biomarkers, particularly AQP4-IgG and MOG-IgG, should be tested in patients presenting with LETM. Serum testing with cell-based assays for these antibody biomarkers are the most reliable and sensitive (more so than CSF), though MOG-IgG results should be used with caution when the clinical presentation is not classic for MOGAD, as false positives do occur with low titers.[19] Clinical judgment should not be replaced with serology alone. CSF studies can be helpful to distinguish MOGAD and AQP4-IgG-NMOSD from MS, with white blood cell counts generally ranging between 0 and 1,000 cells/mm^3 in MOGAD and AQP4-IgG-NMOSD, while usually less than 50 cells/mm^3 in MS. Furthermore, oligoclonal bands are uncommon in MOGAD and AQP4-IgG-NMOSD, whereas 85% of patients with MS will have elevated oligoclonal bands or IgG index.[12]

To date, no randomized controlled trials have been conducted for MOGAD. In the acute setting, expert consensus recommends prompt administration of high-dose IV corticosteroids with IV methylprednisolone 1 g daily for 5 days. In cases with severe neurologic deficits persisting despite steroids, plasma exchange should be considered, or alternatively IV immunoglobulin (IVIG), as this has been used in children with good success.[12,20,21] The role of immunotherapy after an initial presentation of MOGAD remains to be determined, as clinical trials are lacking in this disease. Transient MOG-IgG seropositivity is more often associated with a monophasic course.[14] Therefore, repeating MOG-IgG serum testing can help predict the risk of recurrent disease, although decisions about attack-prevention empiric immunosuppression are generally made on clinical rather than serologic grounds. The current recommended approach is to wait for at least two attacks before initiating long-term attack-prevention immunotherapy with steroid-sparing agents such as azathioprine, mycophenolate mofetil, rituximab, or intermittent IVIG.[22] Prospective, placebo-controlled randomized trials are needed to better guide our chronic treatment approach.

Conclusions and Recommendations

The time to nadir of neurologic symptoms is critical in determining the etiology of a myelopathy, with subacute courses most suggestive of inflammatory myelopathies as seen in MOGAD. Myelopathy in MOGAD is commonly monophasic, though relapses can occur. Ancillary testing with characteristic MRI findings, serologic antibody markers, and CSF analysis are helpful in confirming the diagnosis.

Current expert consensus recommends acute treatment with high-dose IV corticosteroids, and consideration of plasma exchange or IVIG for severe persistent neurologic deficits. Long-term immunotherapy is typically reserved for patients who relapse.

Take-Home Points

- MOGAD can present with a variety of CNS demyelinating features, though typically presentations can include myelitis, optic neuritis, acute disseminated encephalomyelitis, and AQP4-IgG seronegative NMOSD.
- Imaging features suggestive of MOG-IgG-associated myelopathy include LETM that is frequently gray-matter predominant, involvement of the conus, and only subtle or absent contrast enhancement.
- Serum testing for MOG-IgG with cell-based assays is sensitive and reliable, though false positives do occur particularly at low titers.
- Acute treatment for MOGAD involves high-dose IV corticosteroids, and additionally plasma exchange or IVIG for cases with severe persistent neurologic deficits.
- Long-term immunotherapy is reserved for patients with two or more attacks.

Case Presentation 3

A 66-year-old man with a history of rheumatoid arthritis maintained on low-dose methotrexate (7.5 mg once weekly), essential tremor, and hypertension developed the insidious onset of numbness in the lower extremities. Over the course of 3 months, the numbness had ascended to the level of his lower ribs and he had some imbalance, most notably in the dark. He also reported a positive Lhermitte phenomenon. He reported no weakness or bowel or bladder difficulties. He had no systemic or pulmonary symptoms.

He underwent an MRI of the cervical and thoracic spine at a local facility after 4 months of symptoms, and two longitudinally extensive T2-hyperintense lesions were identified in the cervical and thoracic spine with linear dorsal subpial enhancement and the axial "trident" pattern of enhancement (►**Fig. 3A1–A8**). CSF analysis revealed a pleocytosis with white blood cell count of 28 cells/mm^3 (reference range, 0–5) with 94% lymphocytes, an elevated protein of 70 mg/dL (reference range, 15–45 mg/dL), glucose of 48 mg/dL, and negative oligoclonal bands. AQP4-IgG cell–based assay in serum and CSF were negative. Angiotensin-converting enzyme levels in the serum and CSF were normal. He was given a diagnosis of transverse

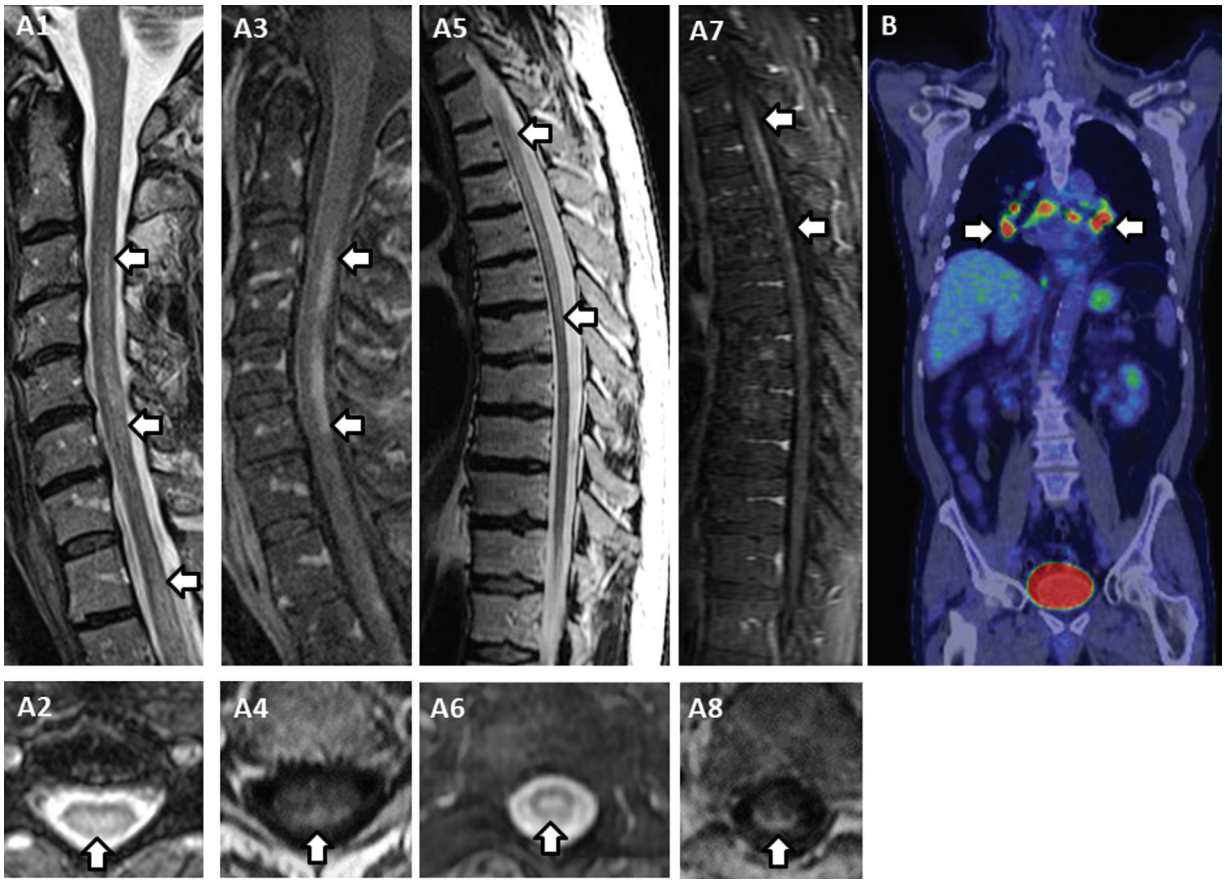

Fig. 3 MRI features of spinal cord sarcoidosis. **(A)** Sagittal T2-weighted and post-gadolinium T1-weighted cervical and thoracic spine MRIs; **(B)** FDG-PET. Sagittal MRI reveals two separate longitudinally extensive T2-hyperintensities extending at least 3 vertebral segments in the cervical and thoracic spine (**A1**, **A5**: arrows) that involve the central cord on axial T2 images (**A2, A6**: arrows). There was accompanying linear dorsal subpial enhancement (**A3, A7**: arrows) that involved the dorsal subpia alone on axial images in the cervical cord (**A4**, arrow) but in the thoracic cord involved the dorsal subpia and central cord forming a three-pronged appearance consistent with an axial "trident sign" (**A8**, arrow). FDG-PET revealed multiple hypermetabolic (red color) lymph nodes in the hilar region (**B**, arrows).

myelitis from AQP4-IgG seronegative NMOSD and given 1 g of IV methylprednisolone once daily for 5 days, followed by five sessions of plasma exchange without clinical improvement.

Repeat MRI approximately 3 months later revealed persistent, although slightly reduced, enhancement. He was then given an additional two sessions of plasma exchange with a plan for completing another course of five treatments, but at that time due to ongoing symptoms he presented to our facility for further evaluation. His neurologic examination revealed spasticity and brisk reflexes in both lower extremities along with positive Babinski signs bilaterally. There was sensory loss to pinprick in both lower extremities without a clear sensory level across the trunk. There was mildly reduced vibration and joint position distally in both feet. His strength was normal and the remainder of his exam revealed a mild action-postural tremor consistent with his history of essential tremor.

Clinical Problem (Localization)

This patient's presentation of an insidiously progressive imbalance, ascending numbness to the ribs, and lower extremity hyperreflexia with upgoing plantar responses is suggestive of a chronic, progressive myelopathy with localization in the high thoracic or lower cervical spine.

Strategies for Evaluation

Diagnostic Reasoning

As discussed in the previous cases, a chronic, progressive myelopathy as in this case warrants consideration of myelopathy etiologies including dural arteriovenous fistula, metabolic myelopathy, neoplastic or paraneoplastic myelopathy, spinal cord sarcoidosis, primary progressive MS, or spondylotic myelopathy. In this particular case, on re-review of the clinical presentation with a myelopathy progressing over months along with the MRI spine features, a diagnosis of spinal cord sarcoidosis was strongly suspected.

Management Recommendations

An 18F-fluoro-deoxyglucose positron emission tomography (FDG-PET) scan was undertaken and revealed multiple hypermetabolic hilar nodes (►**Fig. 3B**). Transbronchial biopsy showed non-caseating granulomas confirming pulmonary sarcoidosis and a diagnosis of probable spinal cord sarcoidosis.

Prognosis

The patient was treated with 1 g of IV methylprednisolone daily for 5 days followed by 60 mg of oral prednisone once daily for 3 months along with trimethoprim-sulfamethoxazole for pneumocystis prophylaxis as well as calcium and vitamin-D supplementation. In addition, his methotrexate was increased to 12.5 mg once weekly and he was given infliximab infusions for both his rheumatoid arthritis and sarcoidosis. MRI of the cervical and thoracic spine showed resolution of all enhancement 3 months later, and the patients' symptoms had not worsened. It was recommended he taper the prednisone slowly over the course of 1 year and he was continued on methotrexate and infliximab for his sarcoidosis and rheumatoid arthritis. At last follow-up, 2 and a half years after diagnosis, he had made some mild clinical improvement and remained on methotrexate and infliximab with a plan to stop the infliximab in the near future.

Applicable Guidelines and Areas of Uncertainty

Spinal cord sarcoidosis can be the initial manifestation of sarcoidosis, and it is important for neurologists to recognize it as it may mimic other disorders.[23,24] Angiotensin-converting enzyme is not a very useful diagnostic tool for diagnosing neurosarcoidosis. A computed tomography (CT) scan of the chest is often recommended as the first step to assess for hilar or mediastinal adenopathy or other changes suggestive of sarcoid. PET-CT can increase the sensitivity for the detection of sarcoidosis beyond CT, and is useful when there is a high suspicion such as in this case.[25] Tissue biopsy revealing noncaseating granulomas is characteristic. A diagnosis of probable neurosarcoidosis can be made with tissue confirmation of systemic sarcoidosis and a compatible neurologic phenotype.[26]

This patient presented with a progressive myelopathy reaching its maximal deficit at 5 months from onset, and thus was inconsistent with transverse myelitis. As discussed previously, inflammatory attacks of myelitis with CNS demyelinating disease such as MS, AQP4-IgG seropositive NMOSD, and MOGAD generally reach their nadir within 21 days.[27] Progression beyond 21 days brings up a broad differential diagnosis of progressive myelopathy.

This patient was diagnosed and treated as aquaporin-4-IgG seronegative NMOSD but did not fulfill criteria for this, particularly as he lacked involvement of other regions (e.g., optic nerve).[28] Indeed, up to half of patients with spinal cord sarcoidosis accompanied by a longitudinally extensive T2-hyperintense lesion are misdiagnosed as idiopathic transverse myelitis or AQP4-IgG seronegative NMOSD.[24] Discriminating spinal cord sarcoidosis from AQP4-IgG seronegative NMOSD is important, as there are important treatment differences despite some overlap. High-dose IV corticosteroids can work for both disorders, but spinal cord sarcoidosis usually requires prolonged high-dose oral steroids for at least 3 months followed by a slow taper over the subsequent 12 months to avoid an early relapse from rapid steroid withdrawal.[24] Plasma exchange is useful for transverse myelitis associated with demyelinating diseases such as NMOSD, but is not used for sarcoidosis. Tumor necrosis alpha inhibitors such as infliximab can be useful in neurosarcoidosis as in this case, but may exacerbate CNS demyelinating disease such as MS.

The gadolinium enhancement pattern in this case was a major clue to the diagnosis. The presence of linear dorsal subpial enhancement extending two or more vertebral segments is strongly suggestive of sarcoidosis and has been shown to be a useful radiologic discriminator between it and NMOSD.[24] Enhancement of the central cord in combination with the dorsal subpial region may form a "trident" appearance on axial images, and, when present, is suggestive of this diagnosis.[29] When educated on the linear dorsal subpial and trident enhancement patterns, these can be identified

readily with excellent agreement among a large group of myelopathies by a neurologist and neuroradiologist.[30] Thus, this is a useful radiologic pearl for neurologists and neuroradiologists to be aware of. The enhancement with spinal cord sarcoidosis tends to persist beyond 3 months even when treated, and this contrasts with CNS demyelinating diseases in which enhancement usually resolves within a couple of months.[24] Clinical and radiologic clues can assist in guiding a clinician toward a diagnosis of spinal cord sarcoidosis.

Conclusions and Recommendations

Clinical and radiologic clues can assist in guiding a clinician toward a diagnosis of spinal cord sarcoidosis. Most importantly, progression of neurologic symptoms beyond 21 days should prompt consideration of alternative causes beyond transverse myelitis including ones that are structural, vascular, other inflammatory (e.g., primary progressive MS, sarcoid), nutritional, neoplastic or paraneoplastic, hereditary, or degenerative myelopathies. Specific gadolinium enhancement patterns (e.g., linear dorsal subpial enhancement, trident sign) can be particularly powerful in differentiating spinal cord sarcoidosis from alternative causes and ultimately guide the clinician to the appropriate disease-directed treatment option.

Take-Home Points

- Progression of myelopathy beyond 21 days is not compatible with transverse myelitis and should lead to consideration of the broad differential diagnoses of progressive myelopathy.
- The presence of linear dorsal subpial enhancement with or without an axial "trident" sign is suggestive of spinal cord sarcoidosis.

Case Presentation 4

A 54-year-old woman with a prior smoking history presented to her local medical center with progressive right lower extremity weakness over the course of 2 to 3 weeks. Given suspicion for an inflammatory myelopathy, she was treated with IV methylprednisolone 1 g daily for 5 days, followed by an oral prednisone taper for 7 days. She noticed significant improvement in her symptoms, but unfortunately a few weeks later she began to develop progressive right lower extremity weakness again. She received a 5-day course of IV methylprednisolone 1 g daily again, though this time with only moderate improvement in symptoms. Approximately 1 month later, she developed progressive right lower extremity weakness a third time, though now with progressive left lower extremity weakness as well. She was referred to our facility for further evaluation. Neurologic examination at that time was notable for a moderate to severe spastic paraparesis in an upper motor neuron pattern, with lower extremity hyperreflexia and upgoing plantar responses. Sensory examination was normal.

Clinical Problem (Localization)

Similar to the other cases, this patient's presentation is suggestive of a myelopathy. With a spastic paraparesis, lower extremity hyperreflexia, and upgoing plantar responses, localization to the thoracic spine is most probable.

Strategies for Evaluation

Diagnostic Reasoning

While one may consider an inflammatory myelopathy given the patient's initial response to IV methylprednisolone, this case has features suggestive of a more chronic, progressive course in comparison with the Case 2, in which the time to neurologic nadir was clearly subacute. Therefore, in addition to inflammatory etiologies, it is important to consider alternative causes including structural, vascular, other inflammatory (e.g., primary progressive MS, sarcoid), nutritional, neoplastic or paraneoplastic, hereditary, or degenerative.

Management Recommendations

MRI of the spine with and without gadolinium revealed a LETM within the thoracic spine, with a unique pattern of tract-specific enhancement along the lateral columns (►**Fig. 4A1–A4**). This pattern can be characteristic of paraneoplastic autoimmune myelopathies.[9,31]

When considering paraneoplastic myelopathy, several neural autoantibodies may be associated, though amphiphysin and collapsin response mediator protein-5-IgG (CRMP-5/anti-CV2) are the most commonly encountered.[9,31,32] In this patient's case, CRMP-5-IgG was positive both in serum and CSF. The remainder of her CSF analysis revealed a pleocytosis with a white blood cell count of 90 cells/mm^3 (reference range, 0–5) with 94% lymphocytes, an elevated protein of 62 mg/dL (reference range, 15–45 mg/dL), normal glucose, and negative oligoclonal bands and IgG index.

An FDG-PET was performed and revealed several hypermetabolic thoracic lymph nodes, with a precarinal lymph node most prominently affected (►**Fig. 4B**). Transbronchial biopsy confirmed a diagnosis of small cell lung carcinoma. She was treated with another course of IV methylprednisolone and initiated on disease-directed therapy for her underlying cancer.

Prognosis

Paraneoplastic myelopathy often portends significant morbidity. With immunotherapy and cancer-directed treatment, some patients may achieve mild improvement or stabilization of neurologic deficits, though often these benefits are not sustained and a large majority of patients become wheelchair bound.[9]

Applicable Guidelines and Areas of Uncertainty

Paraneoplastic myelopathies can occur in isolation or as part of a multifocal paraneoplastic disorder. They are rare and often underrecognized, with a prior study reporting 31 cases of isolated paraneoplastic myelopathy over the course of

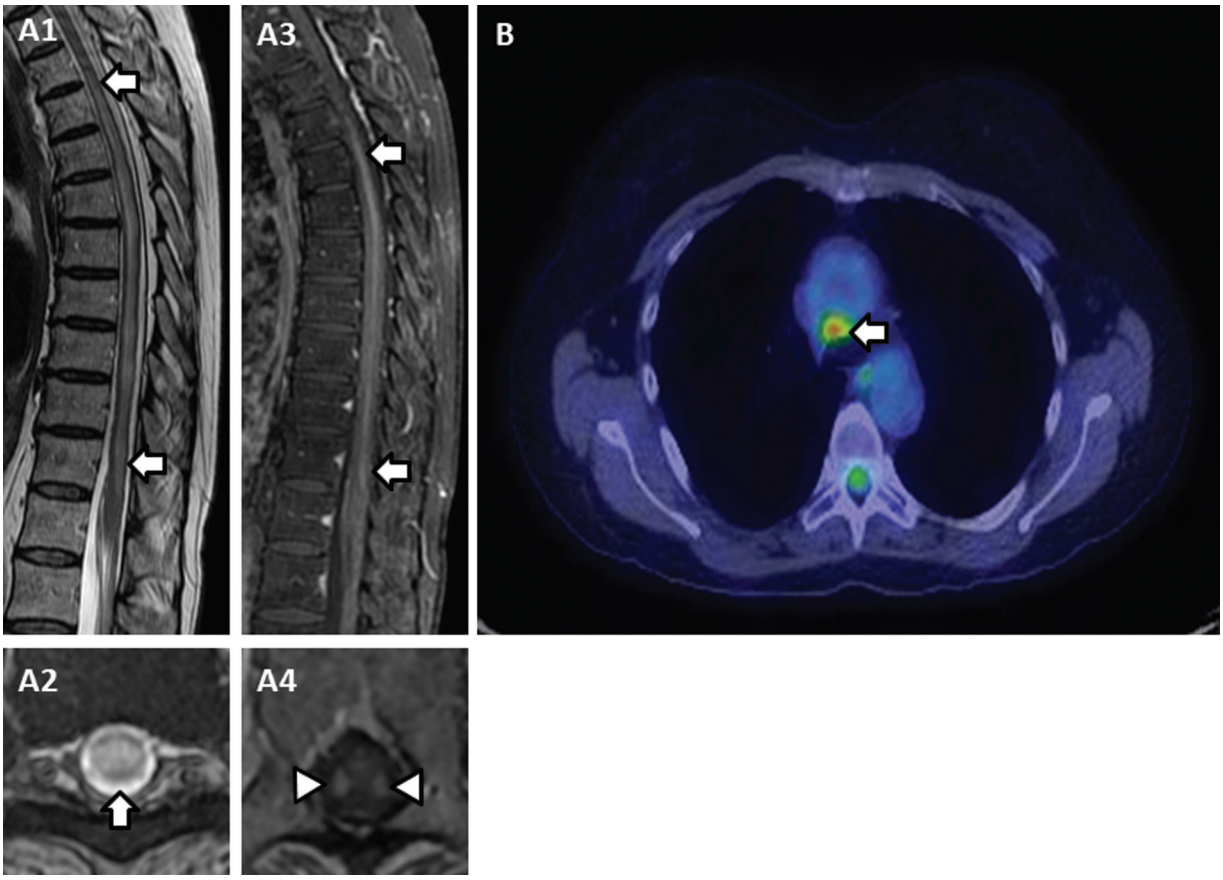

Fig. 4 MRI features of paraneoplastic myelopathy. Sagittal T2-weighted thoracic spine MRI showing a longitudinally extensive T2-hyperintense lesion (**A1**, arrows) involving the central cord on axial T2-weighted images (**A2**, arrow). Sagittal (**A3**) and axial (**A4**) T1-weighted post-gadolinium sequences show a tract-specific enhancement involving the lateral columns (**A3**, arrows; **A4**, arrowheads). (**B**) 18F-Fluoro-deoxyglucose positron emission tomography showing a hypermetabolic (red color) precarinal lymph node (**B**, arrow).

24 years at a high-volume tertiary referral center.[9] While a variety of malignancies may be associated, breast and lung carcinomas, particularly small cell lung carcinoma, are most common.[31] CSF typically reveals a lymphocytic pleocytosis with elevated protein. MRI of the spine reveals a LETM in up to two-thirds of cases, often with a tract-specific gadolinium enhancement pattern that affects the lateral columns (less commonly the dorsal columns). Recognition of tract-specific enhancement in paraneoplastic myelopathy can be of significant utility, by facilitating decisions to search for an otherwise occult malignancy responsible for the myelopathy that often precedes cancer detection.[9] Though CT body is often the first-line consideration to assess for underlying malignancy accompanying a paraneoplastic myelopathy, FDG-PET is more sensitive if suspicion is high.[33]

Conclusions and Recommendations

Chronic, progressive myelopathies should prompt investigation of a paraneoplastic etiology among other considerations, including dural arteriovenous fistula and degenerative, hereditary, primary neoplastic, metabolic, sarcoid, or spondylotic myelopathy. Recognition of characteristic imaging features, particularly a tract-specific gadolinium enhancement pattern, may facilitate earlier diagnosis of an otherwise occult cancer. While immunotherapy and cancer-directed treatment can be mildly beneficial, most patients with paraneoplastic myelopathy unfortunately develop severe neurologic morbidity.

Take-Home Points

- Progression of myelopathy beyond 21 days should prompt investigation of paraneoplastic, primary neoplastic, metabolic, sarcoid, or spondylotic myelopathies among other possibilities.
- The presence of tract-specific lateral column enhancement is suggestive of a paraneoplastic myelopathy.

Case Presentation 5

A 48-year-old man with a history of hyperlipidemia and prior myocardial infarctions was evaluated for lower extremity weakness. He developed the insidious onset of weakness in the lower extremities that progressed steadily over the course of 2 years. He also had weakness in his arms and stiffness in both lower extremities. He reported mild constipation without bladder dysfunction.

He was evaluated at a local medical center and a cervical spine MRI with and without contrast was undertaken, which showed a sagittal T2-hyperintensity extending one vertebral

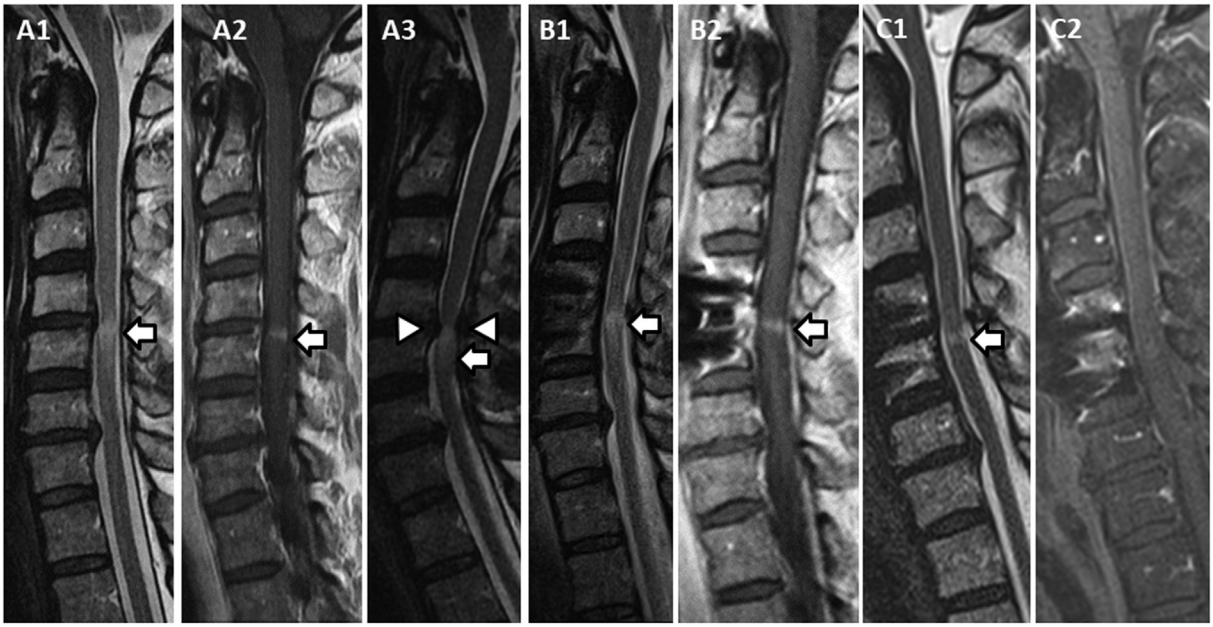

Fig. 5 MRI features of cervical spondylotic myelopathy with enhancement. Sagittal T2-weighted (**A1, A3, B1, C1**) and post-gadolinium T1-weighted (**A2, B2, C2**) cervical spine MRIs preoperatively (**A**), postoperatively at 3 months (**B**), and postoperatively at 12 months (**C**). A preoperative MRI reveals a short T2-hyperintense lesion (**A1**, arrow) with an accompanying pancake-like transverse band of enhancement (**A2**, arrow) with moderate spondylotic changes without obvious compression in the neutral position. MRI undertaken with the neck extended reveals severe spinal cord compression (**A3**, arrow) from spondylotic changes (**A3**, arrowheads). Subsequent postoperative MRIs reveal persistent T2-signal abnormality (**B1**, arrow) and enhancement (**B2**, arrow) 3 months after surgery with less residual T2-signal (**C1**, arrow) and no enhancement (C2) at 12 months postoperatively.

segment with enhancement (►**Fig. 5A1–A3**, **B1–B2**, **C1–C2**). The presence of gadolinium enhancement on spine MRI led to concern for a possible inflammatory myelopathy and thus CSF evaluation was undertaken. However, the CSF was completely normal including white blood cell count, protein, glucose, and negative oligoclonal bands. The diagnosis was uncertain, and he was referred to our facility for further evaluation. Neurologic examination at that time revealed mild weakness of the triceps, finger extensors and interossei, and moderate weakness of the iliopsoas and hamstrings bilaterally. He had hyperreflexia in all four extremities, bilateral positive Hoffmann sign, bilateral ankle clonus, and bilateral flexor plantar responses. Sensory examination was normal.

Clinical Problem (Localization)

With progressive weakness in all four extremities and hyperreflexia throughout, a chronic, progressive myelopathy with localization in the cervical spine is most likely.

Strategies for Evaluation

Diagnostic Reasoning

With a chronic, progressive myelopathy, it is again important to consider myelopathy etiologies beyond those that are inflammatory. The pattern of enhancement in this case (►**Fig. 5**) was suggestive of structural spinal cord compression as seen in spondylotic myelopathy, a cause that would fit the timeline corresponding to the patient's neurologic symptoms.

Management Recommendations

Imaging was repeated with MRI of the cervical spine (►**Fig. 5A1–A2**) which included dynamic flexion–extension views that revealed accentuated spinal cord compression in extension (►**Fig. 5A3**).

Prognosis

With confirmation of cervical spondylotic myelopathy on the additional imaging sequences, the patient was referred to neurosurgery. He subsequently underwent anterior cervical decompression with C4–C5 diskectomy and fusion. Three months after surgery, he reported mild improvement in strength and repeat MRI revealed persistent T2-hyperintensity and enhancement (►**Fig. 5B1–B2**). A subsequent MRI 12 months after surgery revealed resolution of enhancement with mild residual T2-hyperintensity (►**Fig. 5C–C2**).

Applicable Guidelines and Areas of Uncertainty

Cervical spondylotic myelopathy is the most common nontraumatic cause of myelopathy, and thus it is important for neurologists and other clinicians to be aware of some of the less common associated radiologic features. Approximately 15% of patients with cervical spondylotic myelopathy will have accompanying T2-hyperintensity and this is well recognized by neurologists.[34] However, up to 7% can have accompanying enhancement, which often leads to misdiagnosis as tumor or inflammation.[35] The pattern of enhancement in this case was specific for cervical spondylotic myelopathy and generally has

the following characteristics: (1) a transverse band of "pancake-like" enhancement in which the width is greater than or equal to the height; (2) circumferential enhancement of white matter sparing gray matter on axial images (although high-quality axial images were lacking in this case); and (3) the enhancement is at or below the site of maximal stenosis.[10] It is of note that the degree of spinal cord compression may not always be obvious in the neutral position, and dynamic MRI can help reveal an otherwise occult stenosis.[36] This is often misdiagnosed as tumor or inflammation which has risks from inappropriate immunosuppression or unnecessary spinal cord biopsy.[10] Early recognition is important for consideration of definitive surgical treatment. Studies have shown that this enhancement pattern often leads to misdiagnosis, but, among a large group of myelopathies, can be readily identified with excellent agreement by a neurologist and neuroradiologist educated on enhancement patterns.[30]

In follow-up, the enhancement pattern can take months to years to resolve completely, as illustrated in this case.[10] The persistence of enhancement at an early follow-up visit is typical but can lead to diagnostic uncertainty, and in the absence of clinical or radiologic worsening should be recognized to be consistent with this diagnosis.[10] The pathophysiology of enhancement occurring with cervical spondylotic myelopathy is unknown, but may relate to focal breakdown of the blood–spinal cord barrier.[10]

Conclusions and Recommendations

In conclusion, a proportion of cervical spondylotic myelopathies have accompanying gadolinium enhancement that has a specific pattern that physicians should recognize. MRI is very useful in the evaluation of myelopathy to exclude extrinsic compressive etiologies and can help give a clue to the diagnosis.[30] In cases of diagnostic uncertainty, dynamic MRI in extension can help reveal cord compression that is not visible in the neutral position. In this case, the progression of symptoms and MRI findings helped navigate the providers to the correct diagnosis.

Take-Home Points

- The presence of a pancake-like transverse band of enhancement on sagittal cervical spine MRI is suggestive of cervical spondylotic myelopathy.
- Dynamic cervical spine MRI in extension can be useful to reveal cervical cord compression from spondylosis hidden in the neutral position.

Case Presentation 6

A 58-year-old man presented with progressive gait imbalance. One year ago, he started to notice numbness and a cold sensation in his toes that slowly progressed up to his legs to just above the knees over the course of 10 months. In the last 6 months, he noticed more imbalance and a tendency to drag his right foot more than the left. Additionally, he would have occasional leg cramps and episodic abdominal cramps over the same time period. Over the past 2 months, he developed erectile dysfunction, an inability to ejaculate, and both urinary urgency and hesitancy. He denied any symptoms involving his upper extremities.

Neurological examination revealed mild weakness in the bilateral iliopsoas and hip adductor muscles, lower extremity hyperreflexia with upgoing plantar responses, and mildly reduced sensation to temperature and vibration at the distal feet.

Clinical Problem (Localization)

This patient's presentation is suggestive of a chronic, progressive myelopathy with lower extremity weakness, hyperreflexia, and sensory changes suggesting a localization in the thoracic spinal cord.

Strategies for Evaluation

Diagnostic Reasoning

As previously discussed, with chronic, progressive myelopathies, the differential is broad and includes structural, vascular, chronic inflammatory, nutritional, neoplastic or paraneoplastic, hereditary, and degenerative considerations.

Management Recommendations

MRI of the spine was performed and revealed a longitudinally extensive T2-hyperintense signal throughout the thoracic spinal cord (►**Fig. 6**). Laboratory studies revealed normal vitamin B12, copper, and zinc levels in addition to negative AQP4-IgG and MOG-IgG. CSF analysis showed a normal white blood cell count of 1 cell/mm^3 (reference range, 0–5), protein of 84 mg/dL (reference range, 15–45 mg/dL), glucose of 50 mg/dL, and negative oligoclonal bands. FDG-PET of the body and MR angiography of the spinal canal were normal.

Given suspicion for a spinal dural arteriovenous fistula (sDAVF) in the setting of the patient's stepwise progressive myelopathy and a longitudinally extensive lesion in the thoracic spinal cord in an older patient, a digital subtraction spinal angiogram was arranged. This revealed a DAVF at the left S2 nerve root sleeve.

Prognosis

Ablation of the DAVF was attempted during the spinal angiogram but was unsuccessful. The patient then underwent surgical ligation of the fistula with neurosurgery. Thereafter, he had no further progression in symptoms.

Applicable Guidelines and Areas of Uncertainty

sDAVFs typically present with a gradually progressive thoracic myelopathy most commonly in older, male patients. Patients may have Valsalva-associated worsening with abrupt declines, but this does not happen in every patient. Mixed types of pain are commonly seen, and patients may have an exam with apparent peripheral and/or central nervous system findings.[37]

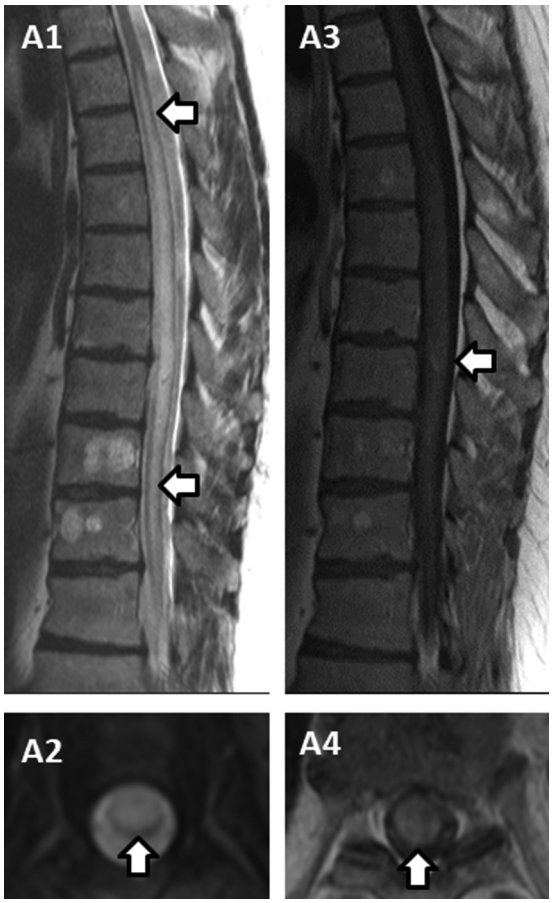

Fig. 6 MRI features in spinal dural arteriovenous fistula. Sagittal T2-weighted imaging shows a longitudinally extensive T2-hyperintense lesion spanning the thoracic spinal cord (**A1**, arrows). Sagittal T1-weighted imaging with gadolinium shows possibly faint contrast enhancement throughout and some vague spots of enhancement (**A3**, arrow). Axial T2-weighted view shows holocord T2-hyperintense signal on cross-sectional view (**A2**, arrow) again with some patchy gadolinium enhancement accompanying (**A4**, arrow).

From an imaging standpoint, this patient did not have any flow voids on the MRI of the spine which are typically seen in about 80% of cases.[38–40] Thus, the diagnosis should still be suspected in the right setting even if flow voids are absent. As a rule of thumb, any myelopathy with longitudinally extensive T2-hyperintense signal in the thoracic spinal cord without a diagnosis found on evaluation should have a spinal angiogram to evaluate for fistula. From a treatment standpoint, if a patient receives corticosteroids for the suspicion of an inflammatory myelopathy when truly they have a sDAVF, an abrupt severe decline in neurological function is often seen.[41] Morbidity in untreated sDAVF is high and often irreversible; thus, it is critical to think of this early as a potential diagnosis. Treatment options include embolization during digital subtraction angiography or surgical ligation of the draining vein. While embolization during angiography may allow avoidance of surgical intervention, efficacy is modestly lower (approximately 70–80%) than a surgical approach (98%).[42,43]

Conclusions and Recommendations

Chronic, progressive myelopathies, particularly thoracic myelopathies in older patients, should raise suspicion for sDAVF as a potential etiology. Spinal imaging with MRI can be helpful, with the majority of sDAVF cases revealing a longitudinally extensive T2-hyperintense signal in the thoracic spine, and up to 80% of cases showing dorsal greater than ventral flow voids corresponding to engorged perimedullary veins. Noninvasive MR angiography can help localize a fistula in many cases, though digital subtraction angiography is the gold standard. Inappropriate corticosteroid administration for suspected inflammatory myelopathy can lead to abrupt worsening of symptoms in sDAVF and therefore should be avoided when the diagnosis is still in question. Treatment options include embolization via angiography or surgical ligation of the draining vein, and can allow for stabilization or improvement in symptoms.

Take-Home Points

- Chronic, progressive thoracic myelopathies, particularly in older patients, should raise suspicion for sDAVF as a potential etiology.
- Digital subtraction angiography is the gold standard in the diagnosis of sDAVF.
- Inappropriate corticosteroid administration for suspected inflammatory myelopathy can lead to abrupt worsening of symptoms in sDAVF and therefore should be avoided when the diagnosis is still in question.

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