A 28-Year-Old Woman With Left-Sided Weakness and Atypical MRI Lesions

From the National Multiple Sclerosis Society Case Conference Proceedings

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Abstract

A 28-year-old woman presented with subacute relapsing left-sided weakness. MRI demonstrated both enhancing C3-C6 and nonenhancing T2-T4 lesions. Initial provisional diagnosis was inflammatory/autoimmune. Her left-sided weakness progressed despite immunosuppressive therapies. We reassessed our original suspected diagnosis because of an atypical clinicoradiologic course, leading to biopsy and a definitive diagnosis.

Case Presentation

A 28-year-old previously healthy woman presented with 7–8 months of progressive left-sided weakness and right-sided paresthesias (Figure 1A). Her symptoms started in October 2021 when she noticed mild weakness in her left arm as well as numbness and tingling in her right arm and leg shortly after a nonspecific mild upper respiratory infection. Her symptoms resolved spontaneously in several weeks, and she did not seek medical attention. In December 2021, she received simultaneous coronavirus disease 2019 (COVID-19) mRNA booster and influenza vaccines and noted some return of left arm stiffness. In late March 2022, after she recovered from a mild COVID-19 infection, she noticed progressive worsening of her left-sided weakness (arm worse than leg) and right-sided paresthesias.

She saw a neurologist in May 2022 where her neurologic examination demonstrated mild 4/5 weakness in the extensor muscles of her left arm and proximal left leg but normal tone throughout. Sensation was intact to pinprick and vibration in her distal extremities bilaterally. Reflexes were more brisk on her left side compared with her right side. Her MRI of the brain was normal, but MRI of the spine revealed an enhancing, expansile T2-hyperintense lateral lesion from C3-C6, as well as what appeared to be a second nonenhancing lesion in the left aspect of the thoracic cord from T2-T4 (Figure 2). She was admitted to the hospital where laboratory evaluation yielded an unremarkable comprehensive metabolic panel and complete blood count, an elevated erythrocyte sedimentation rate of 99 mm/h (normal range 0–30 mm/h), a normal vitamin B12 level, negative antinuclear antibody (ANA) and anti-neutrophil cytoplasmic antibodies tests, and negative screens for syphilis, HIV, and Lyme disease. Serum myelin oligodendrocyte glycoprotein (MOG) and aquaporin-4 (AQP4) antibody tests were negative by cell-based assay (tested twice). CSF showed 3 white blood cells and normal protein and glucose levels. There were no oligoclonal bands. CSF cultures, venereal disease research laboratory test (VDRL), viral studies, and cytology for malignant cells were negative. A CT scan of the chest, abdomen, and pelvis was performed and showed no evidence of sarcoidosis or suspicious masses.
The patient received IV immunoglobulin (IVIG) at 2 g/kg over 5 days with improved clumsiness in her left hand and improved numbness in her right foot. Two weeks after discharge (mid-June 2022), she reported recurrent symptoms with increased difficulty lifting her left hand which prompted readmission. During this admission, she received another course of IVIG along with IV methylprednisolone 1,000 mg daily for 5 days. Again, her symptoms significantly improved. A few weeks later (mid-July 2022), she was seen in our neuroimmunology clinic where she reported return of left arm/hand weakness. Her neurologic examination showed 3/5 strength throughout her left upper extremity. She was given an additional course of high-dose steroids for 5 days (oral prednisone rounded to 1,000 mg daily). After initial improvement with this additional course of steroids, she was readmitted to the hospital in August 2022 secondary to return of left arm/hand weakness. Follow-up MRI revealed persistent enhancement of the cervical cord lesion. She received 2 courses of plasma exchange (5 rounds per course) with partial improvement in strength, although she still had significant weakness in her left arm and hand. Her treatment course is shown in Figure 1B.

Differential Diagnosis

Our patient presented with left-sided weakness and rightsided paresthesias that initially spontaneously resolved within 2 months and then recurred several months later and there-after continued to gradually worsen. Her symptoms coincided with a preceding viral infection each time. Her MRI of the spine demonstrated an enhancing, expansile T2-hyperintense lesion from C3-6 and a nonenhancing lesion in the left aspect of the thoracic cord at T2-T4. The differential diagnosis for her clinical presentation was broad.

The initial etiology was considered to be inflammatory/autoimmune. The presence of 2 spinal cord lesions may suggest a relapsing inflammatory/autoimmune disease, especially when there were both enhancing and nonenhancing lesions present. Moreover, her partial response to several immunomodulatory therapies lent credence to a possible inflammatory/autoimmune cause. Her enhancing cervical cord lesion was left-sided and eccentric (causing a hemicord lesion) that led her to present with a Brown-Séquard syndrome, which could be seen in inflammatory/autoimmune conditions, such as multiple sclerosis (MS), although it should be noted that neoplastic lesions could also rarely cause a Brown-Séquard syndrome. The absence of brain lesions and the longitudinally extensive nature of her cervical cord lesion argued against MS, which tended to favor multiple discontinuous short-segment lesions in the spinal cord.

Neuromyelitis optica spectrum disorder (NMOSD) and MOG antibody-associated disease (MOGAD) could both cause longitudinally extensive myelopathies (≥3 vertebral segments). The enhancement pattern and expansile, edematous nature of the patient’s cervical cord lesion could be seen in acute phases of NMOSD or MOGAD. However, the patient had negative serum AQP4 and MOG antibody testing on multiple cell-based assays. Although seronegative NMOSD could account for her presentation, she did not have any other core clinical characteristic of NMOSD that would fulfill the 2015 NMOSD diagnostic criteria. The criteria for diagnosing NMOSD without AQP4 antibodies required at least 2 core clinical characteristics (acute myelitis, optic neuritis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions, or symptomatic cerebral syndrome with NMOSD-typical brain lesions) resulting from one or more clinical attacks. At least one of the core clinical characteristics must be optic neuritis, acute myelitis with longitudinally extensive transverse myelitis, or area postrema syndrome. The patient only had acute myelitis with longitudinally extensive transverse myelitis and no other core clinical characteristic, so she did not fulfill the diagnostic criteria for seronegative NMOSD. Finally, hypointense lesions on T1-weighted sequences (“T1 dark spots”) could be found in inflammatory/autoimmune conditions, including NMOSD and MS, although our patient’s cervical cord lesion was isointense on T1-weighted sequence (Figure 2).

An inflammatory/autoimmune myelopathy secondary to other etiologies was also considered. The patient’s infectious symptoms just before the initial onset of her neurologic symptoms (as well as her COVID-19 infection just before symptom recurrence a few months later) may point to a possible postinfectious transverse myelitis, possibly related to molecular mimicry between infectious antigens and self-antigens. Neurosarcoidosis, which could frequently involve the spinal cord and may be longitudinally extensive in nature resembling NMOSD, was another consideration. Further neuroimaging features of spinal cord sarcoidosis include dorsal subpial enhancement accompanying the long myelitis and spinal cord swelling. However, neuroimaging features of spinal cord sarcoidosis, including dorsal subpial enhancement accompanying the longitudinal myelitis, were not observed in this patient. Most patients with neurosarcoidosis have systemic involvement, but our patient had no manifestations of systemic sarcoidosis (clinically or on body imaging). It
would also be extremely rare for systemic lupus erythematosus disease to cause only myelitis, although CNS lupus could potentially overlap with NMOSD with associated AQP4 antibodies. The patient’s negative ANA screen made CNS lupus less likely.

The differential diagnosis also included infectious causes. Both neurosyphilis and tuberculosis, for example, could rarely manifest as enhancing longitudinally extensive lesion(s) causing progressive subacute symptoms. However, an infectious etiology was less likely in this patient who had no infectious symptoms or identifiable exposures on presentation of her neurologic symptoms and had an extensive negative workup for infections, including negative screens for syphilis and HIV as well as negative CSF cultures, VDRL, and viral studies.

Finally, the insidious and gradually progressive nature of the patient’s symptoms over many months placed malignancy high on the differential diagnosis list. The Table summarizes the typical clinical and radiologic features differentiating a spinal cord tumor from an inflammatory/autoimmune myelopathy. The patient’s enhancing, expansile cervical cord lesion at symptom onset was concerning for a primary CNS lymphoma or glioma. Like autoimmune/inflammatory myelopathies, primary CNS lymphoma could develop longitudinally extensive spinal cord lesions and would be frequently isointense to hypointense on T1-weighted sequence in addition to high signal intensity on T2-weighted images and enhancement with contrast. Although spinal cord swelling would be typically seen, some patients (approximately 40%) with spinal cord lymphoma could have intramedullary lesions without edema, mimicking a non-neoplastic etiology. Spinal cord gliomas could also develop intramedullary longitudinally extensive lesions. They could cause cervico-thoracic T2-hyperintense spinal cord lesions and diffusely involve the cross-sectional area of the cord with homogenous contrast enhancement. Spinal cord astrocytomas, a type of gloma, could mimic MOGAD-associated spinal cord lesions (including involvement of the conus) but would be distinguished by their eccentric location and irregular margins. Intramedullary spinal cord metastases (the most common of which originate from lung or breast) could mimic inflammatory lesions with a circular border of enhancement on imaging similar to that seen in NMOSD. However, there may be a greater tendency of intramedullary spinal cord metastases to have their circular border of enhancement capped by a flame-like taper on either end, which would not be typical of inflammatory/autoimmune myelopathies. In our patient, the tapering of the expansile spinal cord lesion at the caudal and rostral aspects would be unusual for an inflammatory/autoimmune myelopathy and could favor a spinal cord tumor (Figure 2, A–F). Metastatic spinal cord lesions typically show low signal intensity on T1-weighted images and high signal intensity on T2-weighted images, but our patient’s cord lesion was isointense on T1-weighted sequences (Figure 2). Neoplastic causes of longitudinally extensive myelopathies should be suspected if the patient’s symptoms continued to progress despite treatment with methylprednisolone or plasma exchange or if the patient’s spinal cord imaging showed persistent contrast enhancement after 3 months of onset. A spinal cord biopsy may be necessary to reach a diagnosis.

**Final Diagnosis**

The expansile, gadolinium-enhancing cervical cord lesion and slow progression of symptoms despite multiple courses of immunosuppressive treatments, including IVIG, high-dose steroids, and plasma exchange, led us to pursue a biopsy of the
patient’s cervical cord lesion. She underwent a C2-C7 laminectomy for lesion resection and biopsy in late August 2022. Pathology confirmed a diffuse midline glioma, H3 K27M-mutant, WHO. grade 4 (Figure 2, G–H). Postsurgery, the patient developed loss of sensation in her legs and whole-body tingling. She had difficulty sitting up from lying position. Neurologic examination showed significant 1/5 weakness in her left deltoid, wrist flexors, wrist extensors, and intrinsic muscles of the left hand as well as 0/5 weakness in her left biceps and triceps. She had 4/5 weakness throughout her right arm and left leg and nearly preserved 5-/5 strength in her right leg. She was referred to neuro-oncology and radiation oncology for treatment guidance regarding her diffuse midline glioma.

**Discussion**

H3 K27-altered diffuse midline glioma is a recently described entity first added to the World Health Organization classification of tumors in 2016 that corresponds to a grade 4 diagnosis. These tumors are commonly located in the pons, with only a few cases reported in the spinal cord. A recent study of 35 cases of spinal cord H3 K27M-mutant diffuse midline gliomas identified affected locations spanning cervical (29%), cervicothoracic (20%), thoracic (43%), and thoracolumbar (9%) regions. Prognosis tends to be poor with rapid neurologic decline.

There were several unusual features in our case. First, the presence of the nonenhancing thoracic lesion in addition to the expansile enhancing cervical lesion made us initially concerned for a relapsing course better aligned with an inflammatory/autoimmune, rather than neoplastic, etiology. It was extremely unusual for H3 K27M-mutant diffuse midline gliomas to be multifocal. A recent study found that out of 24 identified diffuse midline glioma cases, all occurred within a single location, and there were no lesions with a clear lack of contrast enhancement. However, intramedullary spinal cord tumors could be multifocal, and there were some cases in the literature of nonenhancing spinal cord tumors, particularly low-grade tumors with a relatively intact blood-brain barrier.
reducing the degree of contrast enhancement. Therefore, multifocal and even nonenhancing lesions could occur with spinal cord tumors.

Another feature of this patient case was that there was initial improvement and response to anti-inflammatory/immunomodulating treatments, including IVIG and high-dose steroids, which led us to consider the possibility of an inflammatory/autoimmune process. However, response to anti-inflammatory treatments may be due to a reduction of CNS infiltrating immune cells after breakdown of the blood-brain barrier from the glioma, which could lead to symptomatic improvement when cord edema is reduced. Spinal cord lymphoma is a different tumor type that is particularly responsive to steroids, resulting in initial, transient improvement of both clinical symptoms and MRI findings. Therefore, a response to steroids did not necessarily support an inflammatory/autoimmune cause. A staccato temporal course and response to steroids could be seen in spinal cord neoplasms.

Ultimately, there were several red flags about the patient’s presentation that suggested a malignancy over an inflammatory/autoimmune myelopathy. Her onset of symptoms was insidious and slowly progressive over the span of 7–8 months, which was concerning for a neoplasm. The time course from symptom onset to maximal severity is generally shorter and more subacute in inflammatory/autoimmune myelopathies. Some infectious myelopathies, such as tuberculous or syphilitic infections, could also present insidiously and should be ruled out, especially if there were any coinciding infectious symptoms. The dissociation between the patient’s initial mild manifestation of her clinical symptoms and the extensive spinal cord lesion observed on MRI could be further suggestive of a slow neoplastic growth over an inflammatory/autoimmune etiology. In addition to a prolonged time course, the patient had an expansile, enhancing spinal cord lesion warranting a high degree of suspicion for tumor. Although an expansile cord lesion could be seen in acute phases of inflammatory/autoimmune conditions, such as NMOSD or MOGAD, it was a red flag when the lesion persistently enhanced after 3 months of onset or when symptoms continued to progress despite anti-inflammatory treatment.

Owing to the above red flags in this patient case, a spinal cord biopsy was obtained to arrive at the correct diagnosis and guide treatment. A spinal cord biopsy should be considered in

Table  Summary of Clinical and Radiologic Features Differentiating Inflammatory/Autoimmune Myelopathy vs Spinal Cord Tumor

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Inflammatory/Autoimmune myelopathy</th>
<th>Spinal cord tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal course of the disease</td>
<td>Acute to subacute</td>
<td>Subacute to gradual/insidious</td>
</tr>
<tr>
<td>Preceding events</td>
<td>Possible history of prior infections or vaccinations immediately preceding the onset of neurologic symptoms</td>
<td>Possible history of primary neoplasm</td>
</tr>
<tr>
<td>Response to immunosuppressive therapy</td>
<td>Symptoms improve</td>
<td>Usually no improvement in symptoms</td>
</tr>
<tr>
<td>CSF features</td>
<td>Lymphocytic pleocytosis</td>
<td>Cell counts are often normal in gliomas</td>
</tr>
<tr>
<td>MRI Variable</td>
<td>Distinguishing feature</td>
<td>Distinguishing feature</td>
</tr>
<tr>
<td>Location</td>
<td>Well-defined and eccentric, commonly in the posterior location, affecting a partial cross-sectional area of the cord, such as in MS</td>
<td>Commonly central or involving the entire cross-sectional area of the cord</td>
</tr>
<tr>
<td>Single or multifocal</td>
<td>Commonly multifocal in the spine and/or brain</td>
<td>Usually a single lesion in the spinal cord</td>
</tr>
<tr>
<td>Distribution</td>
<td>Usually discrete and short-segmented, such as in MS</td>
<td>May be focal or diffuse</td>
</tr>
<tr>
<td>Edema</td>
<td>Usually nonexpansile with minimal edema</td>
<td>Usually expansile with significant edema</td>
</tr>
<tr>
<td>Contrast enhancement</td>
<td>Variable enhancement</td>
<td>Persistent enhancement even after 3 mo of symptom onset</td>
</tr>
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Abbreviations: ADEM = acute disseminated encephalomyelitis; AQP4 = aquaporin-4; MOG = myelin oligodendrocyte glycoprotein; MOGAD = myelin oligodendrocyte glycoprotein antibody disease; NMOSD = neuromyelitis optica spectrum disorder.
patients with progressive symptomatic lesions, when the diagnosis is unclear, or when the clinicoradiologic course is atypical or not behaving as expected after treatment. Although whole-body PET would have been useful to demonstrate hypermetabolism of the spinal cord lesion concerning for tumor, a biopsy was still warranted for histologic characterization and diagnostic confirmation to guide treatment planning. There could be initial reluctance in obtaining a spinal cord biopsy because of fear of an invasive procedure carrying complication risks (as high as 21%) due to collateral injury to the spinal cord.\(^9\) Moreover, spinal cord biopsies could be nondiagnostic, which may increase initial hesitation of undergoing the procedure. While surgeons can microscopically sample tissue from within the cord itself, intramedullary spinal cord biopsies (especially if they also involve resection attempts of the lesion) are typically open spine surgeries through laminectomy and dorsal myelotomy.\(^{20}\) Complications related to open spine surgeries, beyond the risk of neurologic deficits, include postoperative kyphotic deformity requiring additional stabilization surgery (particularly in pediatric cases), wound dehiscence, and infections related to the incision.\(^{20}\) However, careful considerations must be weighed between the potentially large benefits of achieving the correct diagnosis and the smaller risks of the procedure.

In this patient’s case, the initial management strategy was predicated on a working diagnosis of an inflammatory/autoimmune cause. However, her symptoms continued to recur and progress over time, and her expansile cervical cord lesion persistently enhanced even after several months of anti-inflammatory treatment. Therefore, we questioned the original diagnosis, and she underwent a spinal cord biopsy, ultimately revealing a diffuse midline glioma. Our case report highlighted the importance of maintaining an expanded differential diagnosis especially when the clinicoradiologic course was not typical. Invasive diagnostic methods, such as a spinal cord biopsy, may be needed to reach the correct diagnosis in atypical cases.

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Appendix

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<tr>
<th>Name</th>
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