Clinical Reasoning: A 55-year-old woman presenting with ataxia and numbness 1 year after ileum resection

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Neurology® 2019;93:675-679. doi:10.1212/WNL.0000000000008253

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Section 1

A 55-year-old woman developed numbness of the lower limbs, with a distal to proximal gradient, gait instability, severe constipation, and urinary urge incontinence. The symptoms reached their nadir in 20 days. The patient had a history of chronic gastritis. She underwent ileum resection 1 year before for ileitis and she was diagnosed with suspected Crohn disease. The medical history was otherwise unremarkable and at the time of the presentation she was not taking any medication. She denied recent fever or infections.

On physical examination, vital signs were normal and the patient was afebrile. The neurologic examination revealed mild sensory ataxia, with a positive Romberg sign, brisk deep tendon reflexes of the lower limbs, distal tactile hypoesthesia, without a clear sensory level, and altered sense of vibration and position of the lower extremities. Segmental strength evaluation was unremarkable, as was the rest of the neurologic examination.

Questions for consideration:

1. What is the localization of the deficits?
2. Which diagnostic test could be the most informative in this case?

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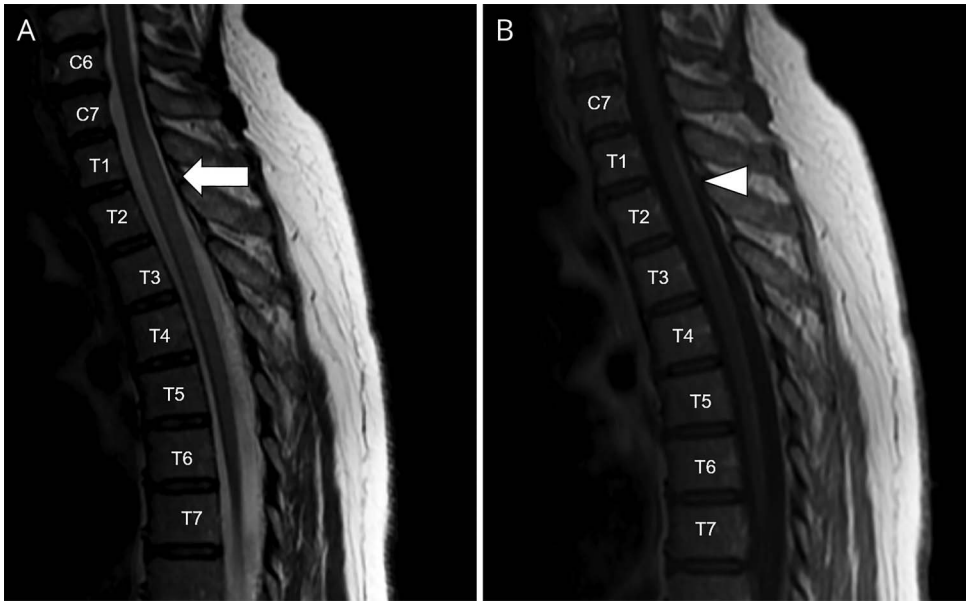
Section 2

Altered superficial and deep sensation at the lower limbs associated with brisk deep tendon reflexes of the lower extremities and sphincter disturbances localize the deficit in the spinal cord. The absence of strength deficit further indicates a predominantly posterior localization of the lesion. An MRI of the spinal cord showed 2 T2/fluid-attenuated inversion recovery hyperintense, central medullary lesions, extended from C2 to C4 and from C7 to T7 (figure, A). Postgadolinium T1 sequences displayed a thin, longitudinally extensive, subpial contrast enhancement (CE) at the C2–C3 and T1–T6 level (figure, B). Brain MRI was unremarkable. CSF examination showed a mild elevation in protein concentration (68 mg/dL, normal range 20–40 mg/dL), with normal glucose and no cells. Blood cells count, liver enzymes, serum creatinine, and thyroid function resulted within normal range.

Questions for consideration:

1. What is the differential diagnosis?
2. What additional diagnostic workup would you perform?

Figure Spinal cord MRI findings



(A) Spinal cord MRI demonstrates, on sagittal T2 sequences, a hyperintense, central medullary lesion, extended from C7 to T7 (arrow). (B) Postgadolinium T1 sequences display a thin, longitudinally extensive, subpial contrast enhancement at T1 to T6 level (arrowhead).

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Section 3

In a case of myelopathy with subacute onset, a broad differential diagnosis has to be taken into account. Considering the anamnestic data of ileum resection, a subacute combined degeneration (SCD) due to vitamin B_{12} deficit needs to be considered. A characteristic MRI finding of SCD is a long spinal cord lesion with symmetrical T2 hyperintensity in the posterior and lateral columns, frequently involving the thoracic cord, though CE is rare.[1] B_{12} blood level resulted within normal range. Copper deficiency can cause a subacute myelopathy that can mimic SCD. Serum copper and ceruloplasmin resulted within normal range. Other metabolic causes to be considered are vitamin E deficiency and zinc excess. The latter resulted within normal range, while the test to assess vitamin E concentration was not available at that time in our institution.

Autoimmune myelopathies should also be considered. Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory autoimmune disease of the CNS that primarily involves the optic nerve and the spinal cord.[2] An inflammatory lesion extending over 3 vertebral segments, namely longitudinally extensive transverse myelitis, is typical, although not pathognomonic of NMOSD.[2] Immunoglobulin G (IgG) autoantibodies to aquaporin-4 (AQP4) are detected in up to 80% of patients with NMOSD.[2] In up to 20% of AQP4-seronegative patients with NMOSD, IgG binding myelin oligodendrocyte glycoprotein (MOG-IgG) is detected.[3] In such forms, the neurologic deficits rapidly develop, reaching the nadir between 4 hours and 21 days after symptoms onset. Moreover, the subpial contrast CE detected by MRI in our patient would be atypical for NMOSD. The patient's serum tested negative on cell-based assay (CBA) for AQP4 and MOG-IgG. Among autoimmune disorders, a myelopathy associated with glial fibrillary acidic protein (GFAP) IgG was considered, but the patient's serum and CSF tested negative for GFAP-IgG by indirect immunofluorescence assay (IFA) on mouse brain sections and CBA.[4] Multiple sclerosis (MS) is an immune-mediated inflammatory demyelinating disease of the CNS. MRI lesions suggestive of MS are typically found in the periventricular region, corpus callosum, centrum semiovale, and spinal cord. However, spinal cord lesions are shorter than those found in our patient and do not show subpial CE. Moreover, brain MRI was unremarkable and CSF examination was negative for oligoclonal bands.

Rarely, a subacute myelopathy may also arise in the context of a paraneoplastic neurologic syndrome (PNS), most frequently associated with collapsin-response-mediator protein 5 (CRMP5) IgG or amphiphysin IgG.[5] Patients' serum and CSF were tested for antibodies specific for onconeural antigens including CRMP-5 and amphiphysin by IFA and immunoblot, but resulted negative. However, it is noteworthy that PNS may occur also in the absence of well-characterized onconeural antibodies.[6]

The subpial CE found on spinal MRI led us to hypothesize a spinal cord sarcoidosis (SCS). Sarcoidosis is an idiopathic multisystem disorder characterized by the formation of discrete, compact, noncaseating epithelioid cell granulomas, that can affect various organs and systems, including the CNS.[7] The concentration of serum angiotensin-converting enzyme (ACE) is frequently elevated in sarcoidosis; nonetheless its role as a diagnostic test is controversial, as its sensitivity and specificity are suboptimal.[8] ACE concentration resulted above normal range (69 UI/L; normal range 8–52 UI/L).

Neurosyphilis and HIV may cause a subacute myelopathy. However, HIV and syphilis serology was negative.

Other possible causes of subacute myelopathy (table e-1, doi.org/10.5061/dryad.0f9m86n) were deemed much less likely considering the characteristics of the MRI findings.

The most probable diagnosis, at this point, was neurosarcoidosis (NS), with paraneoplastic myelopathy considered less likely.

Questions for consideration:

1. What further assessment would clear the differential diagnosis?
2. What is the most likely diagnosis and how would you manage this patient?

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Section 4

A total body CT scan revealed bilateral hilar lymphadenopathy and splenomegaly, but no lesions suggestive of cancer. Pulmonary hilar adenopathy may represent a lymph node localization of an occult neoplasm, potentially underlying a PNS, or may be related to granulomatous inflammation in the context of a systemic sarcoidosis. In order to clarify the differential diagnosis, a transbronchial needle biopsy of the mediastinal lymph nodes was performed. The histopathologic analysis showed non-necrotizing granulomatous inflammation with multinucleated giant cells compatible with the diagnosis of sarcoidosis. The patient was treated with IV methylprednisolone (1,000 mg/d for 5 days) followed by oral prednisone (50 mg daily), with a complete resolution of the bladder and bowel disturbances and a moderate improvement of the sensory symptoms and gait instability. The patient was discharged on oral prednisone therapy, which was slowly tapered to a maintenance dose of 10 mg every other day. Chest CT scan and spinal cord MRI performed 12 months after the disease onset showed a complete resolution of hilar lymphadenopathy and of the spinal cord inflammatory lesions. At the last follow-up, 2 years after the disease onset, the clinical examination showed no neurologic deficits. The patient only reported mild paresthesia of the feet that persists.

Discussion

NS is the involvement, by sarcoidosis, of the central and peripheral nervous system and occurs in 5%–16% of the patients.[9] Evidence of extraneural sarcoidosis can be detected in around 90% of these patients, whereas in the remaining patients the disease is restricted to the nervous system, at least at onset.[7] SCS accounts for around 18% of the neurologic manifestation of NS.[9] The main neuropathologic feature is non-caseating granulomatous inflammation. When the parenchyma is involved, the inflammatory process tends to show a perivascular distribution.[7] The clinical manifestations account on the anatomic substrate affected by the granulomatous inflammation.

As SCS presents similarly to other myelopathy, with a paraparesis or tetraparesis, paresthesia, and bladder or bowel dysfunction, usually with a subacute or chronic onset, the diagnosis may be challenging, particularly in those patients without a history of systemic sarcoidosis.[9] In such cases, MRI is extremely useful in order to suspect this diagnosis. Spinal cord MRI typically shows a linear, dorsal subpial enhancement alone or in combination with a central canal enhancement. When both findings are present, the images resemble a trident head on axial sequences.[10] Intramedullary lesions usually affect cervical or thoracic cord with a mean lesion length ranging from 1 to 9 segments and a posterior or lateral localization.[10] An MRI should also be performed to ascertain brain involvement. Although neuroimaging is greatly useful to support this diagnostic suspect, a pathologic confirmation of a granulomatous inflammation consistent with sarcoidosis is necessary in order to establish a probable or definite diagnosis.[7] The patient described herein underwent a biopsy of the thoracic lymph nodes. Histopathologic findings were consistent with the diagnosis of sarcoidosis. In NS, CSF findings are nonspecific and include pleocytosis, increased protein concentration, presence of oligoclonal bands, and elevated IgG index. CSF ACE concentration has low sensitivity (24%–55%) and high specificity (90%–95%).

The search for an extraneural involvement of sarcoidosis is aimed to the most frequently affected sites and should always include a thoracic CT scan, which may show hilar adenopathy or parenchymal abnormalities consistent with pulmonary sarcoidosis.[7] If the CT scan is negative, gallium scintigraphy or fluorodeoxyglucose PET scan may display otherwise occult areas of inflammation, eventually suitable for a biopsy. It is reasonable to hypothesize that the ileitis was the first manifestation of sarcoidosis in the patient reported; however, we did not have access to the surgical specimen of the patient's ileum to confirm this hypothesis.

NS is a severe disease. Therapy should be start promptly, once the diagnosis is made. Corticosteroids are the mainstay of sarcoidosis treatment.[11] Dose and duration of steroid therapy should be tailored on each patient, according to disease severity and treatment response. Prednisone is commonly started at a dose of 1 mg/kg, and subsequently slowly tapered to a maintenance dose. Immunosuppressive treatment with azathioprine or mycophenolate mofetil can be added as steroid-spearing drug or in those patients who manifest severe or intolerable steroid side effects.[11] In refractory or aggressive cases, second-line therapies such as methotrexate are given. More recently, infliximab, a tumor necrosis factor α inhibitor, showed efficacy in the treatment of steroid-refractory sarcoidosis.[11]

Study funding

No targeted funding reported.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Valeria Cassano, MD	Università Cattolica del Sacro Cuore, Rome, Italy	Author	Acquisition, analysis, and interpretation of data; drafting of the manuscript
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