DIAGNOSTIC AND TREATMENT CHALLENGES | OPEN ACCESS

A young man with numbness in arms and legs

From the National Multiple Sclerosis Society Case Conference Proceedings

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Case presentation

A gentleman in his late 40s developed a "pins and needles" sensation and numbness in his left hand that was exacerbated by leaning on his left arm or hyperextending his neck. The numbness developed over a few weeks. Over the next 2 months, the numbness spread proximally in the left arm, then to the right arm, and in patches over his bilateral upper chest and next to the bilateral posterior thighs. He denied pain, weakness, fatigue, cognitive changes, vision changes, dysarthria, or dysphagia or changes in bladder or bowel function. A review of systems was otherwise negative or normal. Past medical history was notable for hyperlipidemia, treated with atorvastatin 20 mg daily. There was no family history of neurologic or autoimmune disease. Vital signs and general physical examination were normal. Neurologic examination was notable for normal mental status and cranial nerve examinations. Gait, coordination, and the remainder of the motor examinations were normal. Sensation was mildly reduced to light touch circumferentially throughout both arms, in patches over the anterior chest, and over the posterior thighs, with preserved sensation to vibration, pinprick, and temperature. The Romberg sign was not present. Deep tendon reflexes were normal. The plantar response was flexor bilaterally.

Serum testing was negative for aquaporin-4 IgG, and targeted infectious, metabolic, and hematologic studies were unrevealing (table 1). The MRI showed a longitudinally extensive transverse myelitis (LETM, where the T2 hyperintensity extends ≥3 vertebral segments)[1] (figure 1). CSF examination showed no pleocytosis, normal glucose, elevated total protein (84 mg/dL), normal IgG index, and zero oligoclonal bands (table 2).

Differential diagnosis

This patient's symptom onset and evolution were both *subacute*. The differential of a partial myelopathy includes structural (compressive), inflammatory, metabolic, toxic, infectious, paraneoplastic, vascular (especially spinal dural arteriovenous fistula), and malignant causes. Genetic/inherited causes usually present more insidiously.[2] In *acute* cases of myelopathy where inflammation of the spinal cord is demonstrated by imaging or in CSF, but no more specific

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Table 1 Laboratory results: blood

	Result	Reference range
Erythrocyte sedimentation rate	4 mm/h	2–28 mm/h
C-reactive protein	1.5 mg/L	<6.3 mg/L
Antinuclear antibodies	1:160, speckled	<1:40
Anti-proteinase 3	<10 CU	<20 CU
Anti-myeloperoxidase	<10 CU	<20 CU
Smith antibody	<10 CU	<20 CU
RNP antibody	<10 CU	<20 CU
Aquaporin-4 IgG	Not detected	
Vitamin B12, ng/L	388	211–911
Methylmalonic acid, μmol/L	0.19	<0.3
Copper, μg/dL	76	70–140
Alpha tocopherol, mg/L	15.7	5.7–19.9
Beta and gamma tocopherols, mg/L	1.7	<4.3
Lactate dehydrogenase, U/L	94	102–199
Serum protein electrophoresis and immunofixation	Normal pattern/Negative	
HIV antigen/antibody	Negative	
Nontreponemal screen (RPR)	Nonreactive	
Lyme disease antibody total (EIA)	Negative	
Coccidioides antibody immunodiffusion	Negative	
***Bartonella henselae* IgG and IgM**	Negative	
***Bartonella quintana* IgG and IgM**	Negative	
Quantiferon Gold	Negative	

Abbreviations: EIA = enzyme-linked immunosorbent assay; RNP = ribonucleoprotein; RPR = rapid plasma reagin.

etiology is found, the label *idiopathic acute transverse myelitis* may be applied, typically reaching nadir in 4–21 days.[3] This case presented as a subacute partial myelitis.

Table 2 Laboratory results: CSF

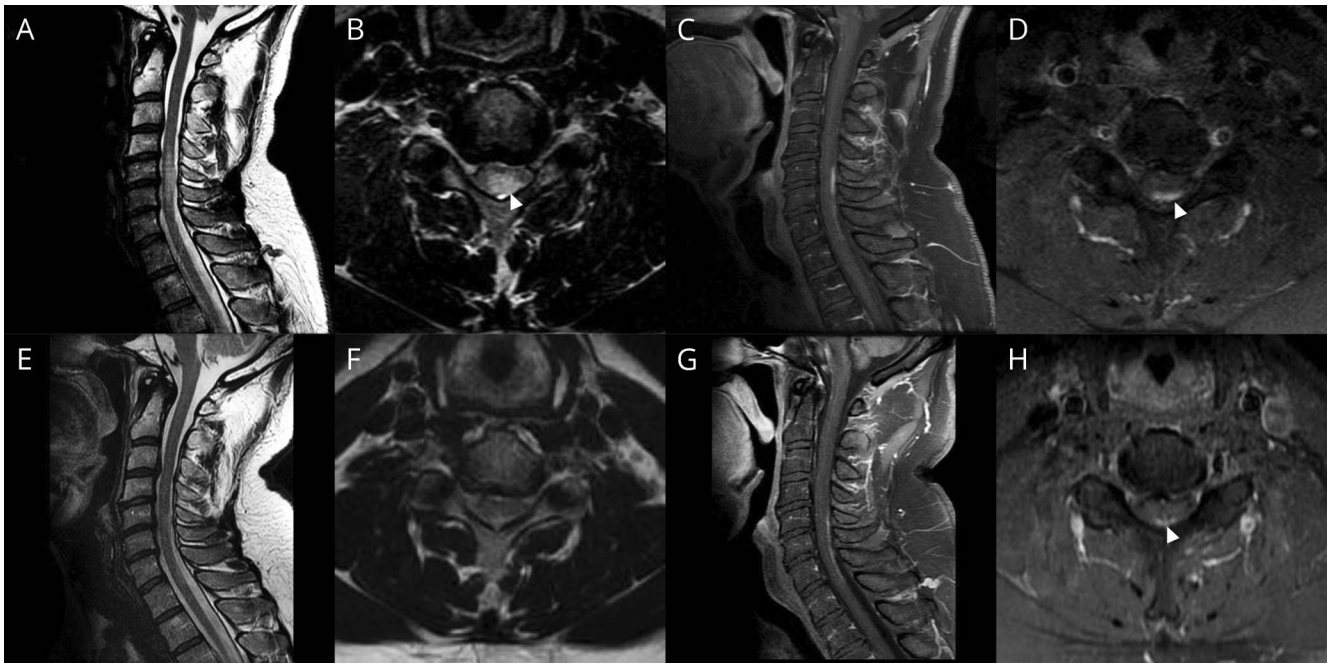
	Result	Reference range
White blood cell count, cells/μL	4	0–5
Red blood cell count, cells/μL	3	0–10
Protein, total, mg/dL	84	15–45
Glucose, mg/dL	53	40–80
Oligoclonal bands	No bands identified	
IgG index	0.49	<0.66
VDRL	Nonreactive	

Abbreviation: VDRL = Venereal Disease Research Laboratory.

A key clinical feature of this patient's presentation is the relative lack of early major clinical deficits despite such an extensive longitudinal spinal cord lesion, which favors neurosarcoidosis, differing from neuromyelitis optica spectrum disorder (NMOSD) pathophysiology (which typically causes extensive tissue destruction all along the lesion, and profound early deficits). While LETM is exceptionally uncommon in MS, it is highly characteristic of NMOSD and can be associated with other inflammatory myelitides, particularly with neurosarcoidosis. Dorsal subpial post-gadolinium enhancement is characteristic of neurosarcoidosis myelitis when compared to NMOSD, whereas the ring configuration of enhancement is highly reminiscent of the inflammatory pattern most commonly affiliated with those diagnostic entities under the rubric of the NMOSD.[4] The "trident sign" describes central canal enhancement with dorsal subpial enhancement in neurosarcoidosis myelitis.[5] This pattern of enhancement can also be seen with CNS infection (including granulomatous infection) and lymphoma.

The circumferential, nondermatomal pattern of sensory loss favors a CNS lesion. The contiguous spread from arms to chest

Figure 1 MRI of inflammatory myelitis before and after treatment



(A and B) Sagittal and axial T2-weighted images that reveal hyperintensity from C4 to C7 involving the central gray and dorsal white matter bilaterally. T1 post-gadolinium images revealed partial, dorsal enhancement of the lesion with likely pial involvement (C and D) with some involvement of the leptomeninges (arrowhead). Repeat MRI after 2 months of oral prednisone (E–H) shows near resolution of the hyperintense lesion previously extending from C4 to C7, but persistent dorsal enhancement likely indicating a nidus of active granulomatous inflammation.

to legs, yet sparing the face, suggests an evolving or expanding cervical spinal cord process below the level of the spinal trigeminal nucleus, which carries pain and temperature as low as C2–C4.[2] The syndrome points towards a *partial* cervical myelopathy with only 1 of the 3 main spinal cord pathways affected (sensory, specifically dorsal column, but not motor or bowel/bladder), as opposed to a true transverse myelopathy.[6]

Given a strong clinical suspicion and high pretest probability for neurosarcoidosis causing his myelitis, a chest CT with IV contrast was performed. The chest CT revealed bilateral hilar and mediastinal calcified lymph nodes and perilymphatic pulmonary nodules, consistent with pulmonary sarcoidosis. Fine needle aspiration revealed rare nonnecrotizing granulomas consistent with sarcoidosis, with no evidence of infection or malignancy.

Final diagnosis

Probable neurosarcoidosis, manifesting as a partial longitudinally extensive transverse cervical myelitis, supported by biopsy-confirmed pulmonary sarcoidosis.

Discussion

Pathobiological mechanisms of noncaseasting granulomatous inflammation

CNS involvement from sarcoidosis occurs in approximately 5%–15% of sarcoidosis patients and can manifest with variable combinations of leptomeningitis, meningoencephalitis, pachymeningitis, optic neuropathy, other cranial neuropathies, hypothalamic/pituitary involvement, myelitis, or radiculitis.[7] While sarcoidosis is classically and formally described as a multisystem disease, about 10%–20% of neurosarcoidosis cases have seemingly exclusive CNS involvement.[7,8]

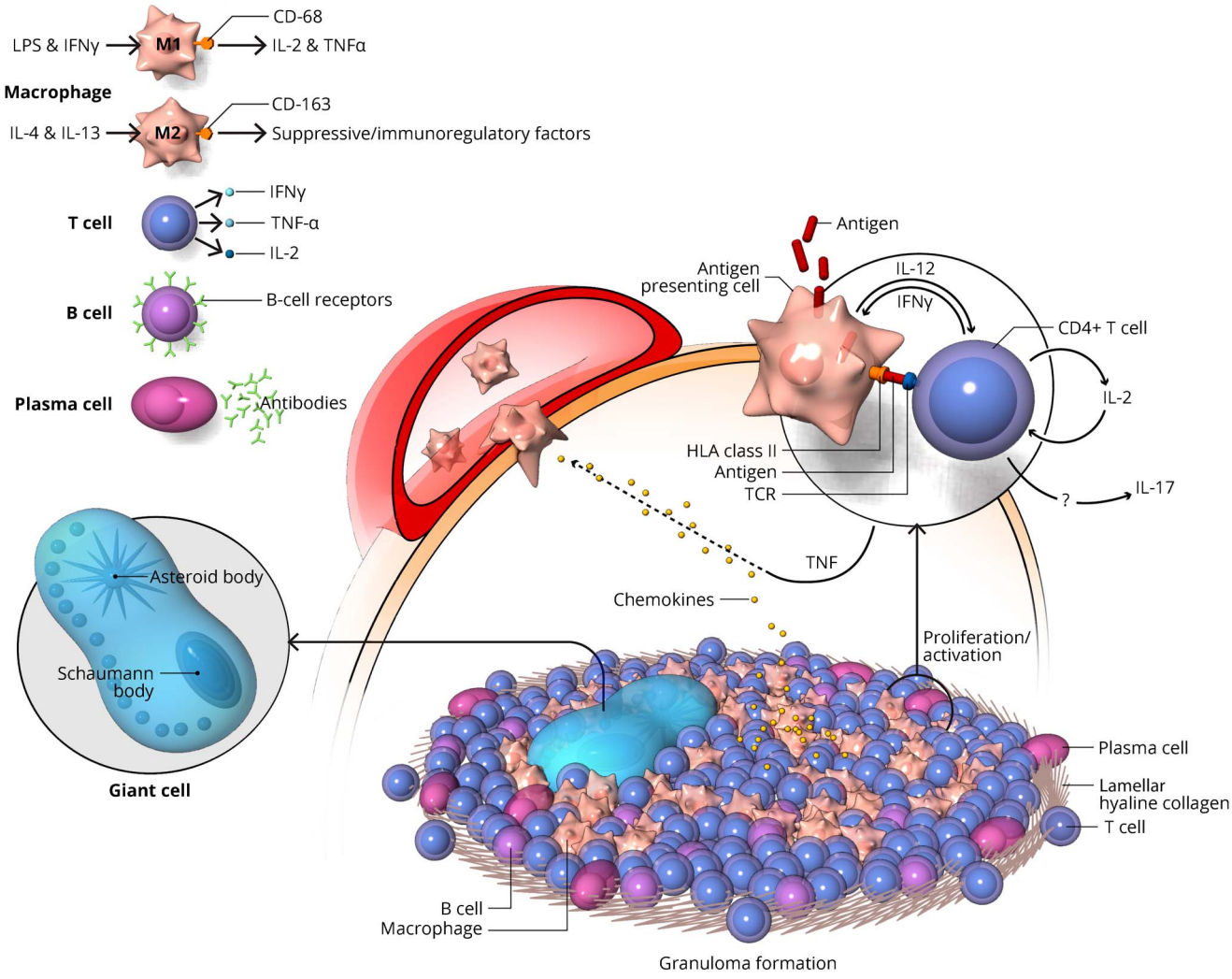
On MRI, neurosarcoidosis spinal cord parenchymal involvement can appear longitudinally extensive, smaller segmental or multifocal.[7,9] In addition to the enhancement pattern seen in this case, there may also be enhancement involving the central canal, nerve roots, meninges, or other parts of the CNS if also affected by neurosarcoidosis.[9] Neurosarcoidosis lesions can exhibit persistent T1 post-gadolinium enhancement for months or years at a time, even with treatment, whereas inflammatory-demyelinating lesions of MS and NMO typically remit within 1–2 months.[4,8,10,11]

Our patient's chest CT revealed bilateral hilar and mediastinal calcified lymph nodes and perilymphatic pulmonary nodules, consistent with pulmonary sarcoidosis. If the CT is negative, a whole-body Fludeoxyglucose Positiron Emission Topography (FDG-PET) can be diagnostically valuable to look for metabolically active but still normal sized lymph nodes that may be targets for biopsy. A skin examination looking for evidence of cutaneous sarcoidosis and eye examination (and sometimes conjunctival biopsy) may also be helpful in this context.

Angiotensin-converting enzyme (ACE) level is commonly considered in the diagnostic evaluation for sarcoidosis, but it is a nonspecific marker. While serum ACE tends to be higher on average in patients with sarcoidosis (and especially active pulmonary sarcoidosis) compared to those without sarcoidosis, sensitivity for sarcoidosis is low, 29%–60%, with specificity of about 89%.[12–15] Similarly, in the CSF, sensitivity and specificity of ACE for neurosarcoidosis are 24%–55% and 94%, respectively.[16,17] In summary, a normal ACE should not exclude neurosarcoidosis, and an elevated ACE can be nonspecific and sometimes seen in association with other inflammatory, infectious, malignant, or metabolic processes or polymorphisms in the ACE gene.

The inflammation of sarcoidosis is characterized by well-formed, noncaseating (nonnecrotizing) granulomas containing monocytes and macrophages, T lymphocytes, B lymphocytes, and fibroblasts, among other cell types (figure 2).[18,19] Granulomas in the CNS tend to have a perivascular predilection. The granulomatous inflammation of sarcoidosis

Figure 2 Putative mechanisms of noncaseating granulomatous inflammation in neurosarcoidosis



This figure illustrates putative mechanisms the assembly and organization of the complex coordination of putative cellular and molecular mechanisms, which are thought to represent the pathobiological underpinnings for noncaseating granulomatous inflammation in neurosarcoidosis. Immune cells traffic into the "target tissue" via arterioles and can subsequently exhibit properties of antigen presentation. A collection of various immune cell types (e.g., B and T cells, macrophages, and plasma cells) acquire an affinity to become part of what we analogize as an "island of inflammatory cells," delimited by a perimeter principally composed of hyaline collagen (shown on the figure). As opposed to granulomatous inflammation associated with tuberculosis and other processes, those compositional cellular elements in sarcoidosis usually do not undergo necrotic granulomatous transformation. The M1 designated macrophage is an important constituent of the sarcoid granuloma, and most particularly with respect to its ability to coordinate the inception and prolongation of "pro-inflammatory" cascades, thereby representing a key feature of the noncaseating granuloma of sarcoidosis. Alternatively, the M2 macrophage is characterized by its ability to provide reciprocal properties, in striking contradistinction, to the M1 macrophage, by exhibiting cardinal anti-inflammatory characteristics, including, but not limited to, the elaboration of a highly stereotyped set of anti-inflammatory cytokines and chemokines. Taken together, the repertoire and heterogeneity of intragranulomatous mononuclear cells serve to orchestrate the immune regulatory networks that provide for both the ignition and the complex coordination of the cellular and humoral factors, which have now become classic hallmarks of granulomatous inflammation. The noncaseasting granuloma is equipped with counterbalancing mechanisms (i.e., the inflammatory "braking system") capable of both high precision attenuation, as well as a corresponding ability to abolish those cascades that serve to provoke and perpetuate granulomatous inflammation in nearly every organ and tissue within the human body. TCR = T cell receptor.

is primarily T cell mediated, and classically considered Th1 driven, but emerging evidence promotes a Th17-driven process, at least in the lungs and mediastinal lymph nodes.[20,21] Common cytokines involved in signaling in sarcoidosis include IFNγ, TNFα, and various interleukins and chemokines.[18,19] Environmental and infectious exposures have been proposed as possible contributors to sarcoidosis susceptibility, but none have yet been convincingly demonstrated.[19] Genetic susceptibility to sarcoidosis has been associated with specific human leukocyte antigen alleles, supporting an autoimmune etiology.[19]

Several proposed diagnostic approaches to neurosarcoidosis have been used in the literature over the years.[22,23] Updated consensus diagnostic criteria for neurosarcoidosis were published in 2018.[24] Diagnosis of "definite" neurosarcoidosis is supported by a confirmatory biopsy from the nervous system consistent with sarcoidosis in the context of a consistent clinical phenotype and rigorous exclusion of other causes, particularly infection and malignancy. However, CNS biopsy is often not preferable or advisable due to risk of morbidity. A diagnosis of "probable" neurosarcoidosis, as in this case, can be made with a syndrome consistent with granulomatous inflammation of the CNS and a confirmatory biopsy of sarcoidosis from another organ system. Cases in which sarcoidosis is suspected but in which there is no biopsy confirmation are best designated as "possible" neurosarcoidosis.

There are no randomized controlled trials of treatment of CNS neurosarcoidosis. While glucocorticoids are effective for most patients with neurosarcoidosis, the doses needed to achieve or sustain remission can be prohibitive due to glucocorticoid toxicity.[22] Common steroid-sparing therapies in clinical practice include methotrexate, azathioprine, mycophenolate mofetil, leflunomide, hydroxychloroquine, and, increasingly, infliximab.[25] Retrospective analyses suggest that mycophenolate mofetil may be less effective than methotrexate (at least for preventing "relapse"), but such studies risk confounding by indication.[25,26] In retrospective analyses, infliximab, a TNFα inhibitor, is associated with favorable outcomes, including some cases refractory to other therapies.[8]

In the patient presented here, given concern about glucocorticoid adverse effects, the patient elected to initiate infliximab with weekly oral methotrexate and tapered off glucocorticoids completely within 4 months with gradual resolution of symptoms without functional limitation. Surveillance MRIs at 7 and 12 months showed complete remission.

Author contributions

A.R. Romeo: conception, drafting of manuscript, critical revision of manuscript. S.S. Zamvil and R.P. Lisak: conception, critical revision of manuscript for intellectual content. E. Meltzer, E.J. Fox, E. Melamed, A. Lucas, L. Freeman, T.C. Frohman, and K. Costello: critical revision of manuscript for intellectual content. E.M. Frohman: conception, critical revision of manuscript for intellectual content, along with the design and development of figures 1 and 3 in collaboration with the medical illustrator Mr. Jason Ooi. J.M. Gelfand: conception and critical revision of manuscript for intellectual content.

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