CLINICAL PRACTICE
Clinical Reasoning

Off Trail, On Track: an Exercise in Clinical Reasoning

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In this series a clinician extemporaneously discusses the diagnostic approach (regular text) to sequentially presented clinical information (**bold**). Additional commentary on the diagnostic reasoning process (*italic*) is interspersed throughout the discussion.

A 55-year-old man presented with difficulty walking.

Difficulty walking is a non-specific descriptor that can result from a myriad of problems anywhere along the neural axis, from the central and peripheral nervous system to the neuromuscular junction and muscle. Metabolic disturbances, endocrinopathies, paraneoplastic processes, and infectious diseases can affect the neural axis at each of these levels. Pathology outside of the nervous system such as arthritis, angina, claudication, or dyspnea can also be implicated. A detailed history and exam are needed to focus the differential.

To approach the undifferentiated problem of "difficulty walking," the discussant activates a diagnostic schema, a cognitive tool used to systematically approach a complex clinical problem. She starts by describing an anatomic approach to a neurologic problem, considering systems that affect the neural axis. However, she does not anchor on nervous system pathology, and considers musculoskeletal, cardiovascular, and respiratory issues as well.

Three months prior, the patient was in his usual state of health, hiking and riding his bike on the trails of Northern California. He initially developed intense pruritus over his mid-ulnar forearms, which progressed to numbness and tingling that spread distally over one week to include the ulnar side of his wrists, hands, and fourth and fifth digits, but spared his remaining fingers. He had difficulty grasping objects as the involved fingers "felt stuck." A month into these symptoms, he noticed numbness of all of his toes, both feet and ankles. He was unable to walk due to "not knowing where [his] feet [were]," and had "tightness and spasms" of his calves and thighs. He felt off balance when standing, but had no falls. He had no joint pain. His hands and feet felt uncomfortably "tingly." On review of systems, he had new constipation and straining with urination. He had no fevers, chills, night sweats, weight loss, rashes, joint swelling, chest pain, dyspnea, changes in vision, polyuria, polydipsia, or diarrhea. He had no recent vaccinations, nor was he able to recall any illnesses prior to symptom onset.

Symmetric sensory symptoms like itching and tingling in a stocking-and-glove distribution can suggest damage to sensory nerve fibers (length-dependent peripheral polyneuropathy), most commonly from diabetes, chronic alcohol use, vitamin B_{12} deficiency, or HIV. However, in typical length-dependent peripheral polyneuropathy, symptoms are noted in the feet and ankles first, followed later by symptoms in the hands, given the relative lengths of the axons innervating the limbs. Further, with diabetes, B_{12}, and alcohol-related polyneuropathies, symptoms tend to progress slowly, and I am struck by the rapid onset and progression of these symptoms, as well as bowel and bladder dysfunction.

Given the progressive, severe, near simultaneous expression of symptoms in the upper and lower extremities, primarily ulnar distribution in the arms, along with bowel and bladder dysfunction, lesions of the nerve roots (radiculopathy), spinal cord (myelopathy), or both (myeloradiculopathy) must be considered, particularly in the cervical area, given arm involvement. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP), also called Guillain-Barré syndrome (GBS), and chronic inflammatory demyelinating polyneuropathy (CIDP) should be considered. However, they are often associated with more prominent weakness; sensory findings may be present, but are typically milder. Vasculitis, a potentially life-threatening diagnosis, should also be considered. While vasculitic neuropathy commonly presents as multiple mononeuropathies (mononeuropathy multiplex)—pathology in more than one named large fiber nerve in separate areas of the body—it can mimic a polyneuropathy when rapid in onset or when overlapping neuroanatomic involvement present. Small vessel vasculitis (e.g., in cryoglobulinemia) typically presents in a more

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symmetric fashion and should be considered. Paraneoplastic neuropathies, which can present before malignancies are identified, and hyper- or hypothyroidism also are important possibilites. Finally, given outdoor exposure, he is at risk for zoonotic, tick- and mosquito-borne infections. West Nile is classically associated with flaccid paralysis from anterior horn cell injury in the spinal cord. A detailed exam, with motor, sensory, and cerebellar testing, is critical to determine whether weakness is present and whether there are signs localizing the lesion to the peripheral nerves, roots (including absent reflexes), or the central nervous system.

Based on the initial history, the discussant forms a problem representation—a succinct description highlighting key features of the presentation—to try to match the case to an illness script. An illness script is a clinician's mental summary of a disease, including predisposing factors, clinical features, time course, and pathophysiology. Initially, the problem representation triggers consideration of a familiar cause of stocking-and-glove sensory symptoms: length-dependent peripheral polyneuropathy. However, the discussant notes features of the presentation that do not fit that script (the progressive, severe, near simultaneous expression of symptoms in the upper and lower extremities, primarily ulnar distribution in the arms, along with bowel and bladder dysfunction) and uses those clues to consider alternative anatomic localizations. Her new problem representation evokes a new schema with several diagnostic categories: inflammatory, infectious, metabolic, and paraneoplastic. The discussant stresses the need for a detailed neurologic exam to localize the lesion and demonstrates a hypothesis-driven approach by calling out parts of the exam that will be pivot points in her diagnostic thinking (weakness/absent reflexes). Practice and reflection are required to recognize when a case does not fit an initial diagnostic consideration. Re-framing patients to highlight features that do not fit the first diagnosis triggered can defend against common cognitive traps like premature closure, anchoring and availability bias.

The patient had a remote history of traumatic brain injury from a bicycle accident, which was characterized by now resolved transient memory loss. He used no medications. He worked as an engineer and lived inland in Northern California with his family. He did not smoke tobacco and drank one can of beer daily. He was monogamous with his wife and reported no substance use. There was no family history of neurologic disorders.

His occupation as an engineer may put him at risk for contact with harmful chemicals such as heavy metals including lead, arsenic, or mercury, which could be implicated here. A detailed occupational history should be taken. Given the rapid progression of symptoms, evaluation must proceed quickly.

Determining whether the social history is relevant to the chief complaint can be challenging. Risk factors for disease are key parts of illness scripts and can trigger new diagnostic possibilities. Here, potential exposures suggested by the social history spark new ideas and a call for a careful occupational history. The discussant also emphasizes the need for urgent evaluation—often, in complex cases, in parallel with diagnostic thinking, clinicians must determine the appropriate pace for the work-up.

On physical examination, his vital signs were normal. He appeared mildly anxious. His cardiopulmonary, abdominal, musculoskeletal, and skin exams were normal. On neurologic examination, he had normal speech, was fully oriented, and had intact memory. Cranial nerves II to XII were intact. Power in the upper and lower extremities was full. He had spasticity in his lower extremities. There were no fasciculations, nor tremors. Sensation to light touch was diminished in patchy areas over the upper chest, abdomen, back, and diffusely over the ulnar aspect of the forearms starting at the elbows, down to the lateral wrists, hands, fourth and fifth fingers, and over the lateral aspects of the legs bilaterally starting at the knees, extending down to involve the ankles, feet, and toes diffusely. Vibration sensation was decreased in all toes, lateral malleoli, and the phalangeal joints of the fourth and fifth digits of both hands only. Toe and ankle proprioception was impaired. Perirectal sensation and rectal tone were normal. Pinprick and temperature testing were not performed. He had no dysmetria on finger-to-nose or heel-to-shin testing. Babinski sign was negative. Patellar and bicep reflexes were brisk. He had four beats of clonus on the right foot and two beats on the left. His gait was wide-based and he swayed on Romberg testing.

The exam is very helpful and points to a central nervous system localization. Problems with light touch, vibration, and proprioception involving the trunk suggest involvement of the dorsal columns of the spinal cord. It would be helpful to know if pain and temperature sensation are affected as spinothalamic tract involvement could help our localization. Despite the negative Babinski, we have enough data (e.g., brisk patellar and bicep reflexes, clonus, bowel and bladder symptoms, truncal sensory changes, and spasticity in the lower extremities) pointing toward a progressive cervical myelopathy (given upper extremity involvement) that urgent imaging of the cervical cord is warranted. Spinal cord pathology is often time-sensitive, so imaging should not be delayed. While a severe/transection-type lesion in the cervical cord would lead to a "cape-like" symptom distribution involving the neck, shoulder, trunk, and lower extremities, with a sensory level below the level of the lesion, a partial cervical lesion can lead to patchier deficits in the upper and lower extremities as in this case. Given evidence of dorsal column dysfunction, testing for syphilis could also be considered; however, the time course is too rapid for neurosyphilis and this diagnosis is exceedingly rare in the current antibiotic era.

Given this patient's progressive and debilitating symptoms, I would strongly consider a neurology consult—their expertise will be critical as we work to quickly localize this patient's lesion and plan our next steps.

The neurologic exam leads the discussant to shift her focus to a central nervous system process. Her script for spinal cord lesions includes not only the textbook transection–type lesion, but also the patchier picture seen with partial cervical lesions. She notes the dangerous and time-sensitive nature of cord pathology, and advocates for urgent imaging. Additionally, the discussant, an internist, seeks to expand the diagnostic team to include a neurologist. Diagnosis is often a team-based activity, and humility in the diagnostic process is a marker of clinical maturity. Gathering additional expertise is particularly relevant when a patient's symptoms are progressing rapidly and when a diagnostic delay could result in increased morbidity.

Complete blood count, chemistry, and liver panels were normal. Serum protein electrophoresis, serum-free light chains, hemoglobin A1C, vitamin B_{12}, and TSH levels were normal. Plasma RPR and HIV antibodies were negative. Bilateral median and ulnar motor nerve conduction studies showed ulnar neuropathies up to the elbows. An MRI of the cervical spine with gadolinium showed a 2.4-cm nodular, gadolinium-enhancing mass lesion centered at C4/C5 with surrounding cord edema extending from C1 to T4 with predominant dorsal column involvement (Fig. 1). The patient was admitted to the hospital for biopsy of the mass.

These imaging findings represent a major turning point. The mass explains many of the patient's symptoms and findings, and our focus must now shift to determining its underlying cause. The lesion is characterized as an intramedullary mass, referring to its location within the dural layers. While extradural masses are often due to cystic outgrowths of the meninges or benign nerve tumors, intradural masses can be due to autoimmune demyelinating conditions (e.g., multiple sclerosis, acute transverse myelitis), malignancies (e.g., primary CNS and metastatic cancers), inflammatory/infiltrative diseases (e.g., vasculitis and sarcoidosis), and infections (e.g., coccidioidomycoses, West Nile, and herpes myelitis). Neurosarcoidosis and malignancy are important possibilities. Chronic infections such as coccidioidomycosis, a consideration since the patient lives near the Central Valley of California, are less likely to cause this degree of illness in an immunocompetent patient. We do not have a clear exposure history for tuberculosis, and with tuberculosis in the CNS, I would expect the patient to be sicker. Toxic metabolic causes are eliminated as they do not present with mass lesions. While obtaining tissue for pathology and culture is tempting, a biopsy would be high risk, given the location of the mass. Alternative diagnostic options should be sought. A lumbar puncture with routine testing plus pathology as well as bacterial, fungal, and mycobacterial cultures would be a reasonable next step.

The discussant uses the newly discovered cervical lesion as a pivot point and activates another diagnostic schema for intramedullary spinal cord masses narrowing her diagnostic considerations of demyelinating, malignant, inflammatory, and infectious causes to malignancy and neurosarcoidosis. A pivot point is a diagnostic clue that has a limited differential diagnosis and can be used to focus the differential to solve a challenging case.[1,2] *Given the risk of a biopsy in this location, she settles on lumbar puncture as a more appropriate next step.*

A lumbar puncture revealed an opening pressure of 21 mm H_2O, glucose 72 mg/dL (serum 135 mg/dL), protein 63 mg/dL, 4 white blood cells (87 lymphocytes, 13 monocytes), and 2 red blood cells. Analysis of cerebrospinal fluid (CSF) by flow cytometry and pathology did not reveal a monoclonal lymphoproliferative disease, and bacterial, fungal, and mycobacterial cultures were negative. In preparation for surgery, a computed tomography (CT) scan of the cervical spine with intravenous contrast was performed, which showed the previously described spinal lesion as well as bilateral hilar masses. Surgery was canceled. A CT scan of the chest, abdomen, and pelvis with intravenous contrast revealed bilateral hilar lymphadenopathy (Fig. 2), but no other abnormalities.

Chronic infections such as CNS tuberculoma or coccidioidomycosis are very unlikely given the lack of a CSF pleocytosis. Lack of atypical cells on pathology and flow cytometry makes malignancy less likely. CSF findings in neurosarcoidosis are variable; while abnormalities are often seen, his fairly normal CSF profile does not rule out this diagnosis. Evaluating for oligoclonal bands and an IgG index would be helpful, as they may be elevated in neurosarcoidosis. Moreover, the CT showing hilar lymphadenopathy without signs of metastatic disease raises neurosarcoidosis to the top of my differential. A biopsy is of highest priority. His enlarged hilar lymph nodes may be accessible via bronchoscopy and would be a far safer site for biopsy compared to the cervical mass.

The discussant adds the bilateral hilar lymphadenopathy to the spinal cord mass and myelopathy in her problem representation to triangulate her diagnostic considerations, propelling neurosarcoidosis to the top of her differential. She also notes a more attractive biopsy site.

Serum Quantiferon Gold release assay was negative for latent tuberculosis. Sputa staining for acid fast bacilli was negative. Serum LDH, calcium, 1,25-OH vitamin D, and 24-h urine calcium were normal. Peripheral blood flow cytometry, coccidioidomycosis complement fixation, and immunodiffusion were negative. The patient underwent endobronchial ultrasound with biopsies of the left hilar lymph node. Pathology showed non-caseating granulomas with negative stains and cultures for bacterial, mycobacterial, and fungal elements. Flow cytometry of the biopsy specimen was negative for a monoclonal cell population.

The combination of the hilar lymph node biopsy showing non-caseating granulomas with negative stains and cultures for mycobacteria and fungi, and the lack of a monoclonal cell

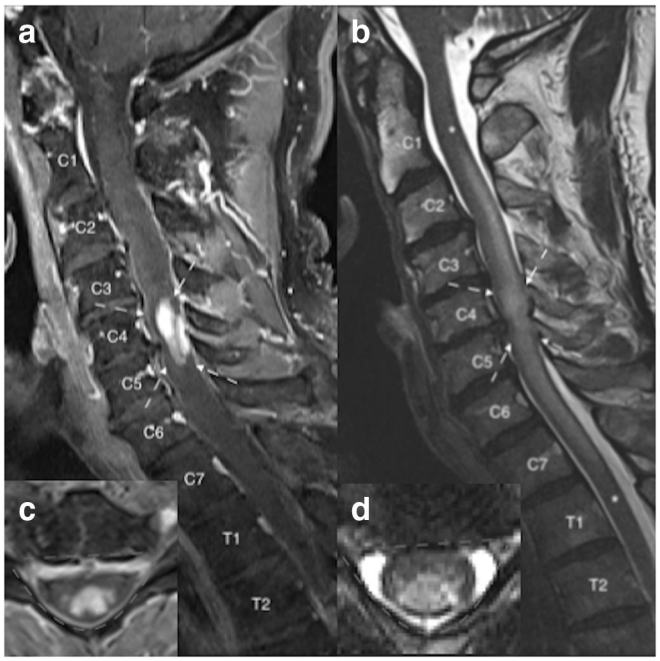

Figure 1 Magnetic resonance imaging (MRI) of the cervical spine showing sagittal views of a T1-weighted, gadolinium-enhanced (panel a) and T2-weighted (panel b) intramedullary C4/C5 cervical cord mass (arrows) and surrounding edema (the asterisk symbol denotes the edges of the enhancement). Axial views of gadolinium-enhanced, T1-weighted (panel c) and T2-weighted (panel d) images at the level of C4/C5 showing dorsal column predominant involvement by the mass.

population makes neurosarcoidosis the most likely diagnosis. While hypercalcemia, elevated urinary calcium, and high vitamin D levels can be seen in sarcoidosis, none of these findings are highly sensitive for the diagnosis and their absence does not substantially reduce its probability.

The mainstay of treatment for neurosarcoidosis is immunosuppression with high-dose corticosteroids. Due to the risk of prolonged immunosuppression, chronic hepatitis B and C infection should be ruled out. It will be critical to have a multidisciplinary meeting with this patient and his support network to explain this complex diagnosis and the next steps in his care, acknowledge emotion, and answer the many questions he is likely to have. The goal of neurosarcoidosis treatment is to achieve and maintain symptom remission. The patient is unfortunately starting on a journey of chronic illness that will require a trusting relationship with the healthcare team. Setting a tone of collaboration at the start of this treatment will be vital to his long-term health.

The discussant reviews her illness script for sarcoidosis. While the patient is missing some of the "classic" findings of sarcoidosis, her knowledge of the imperfect sensitivity of these findings allows her to accept the diagnosis. She also recognizes the importance of engaging the patient and family by providing education on a new and complex diagnosis, and fostering a trusting relationship with the healthcare system. It is important to be mindful that while diagnostic puzzles captivate our "Sherlock Holmes" instincts, just as much attention must be paid to effective communication with patients and their families about their diagnoses. Diagnosis is only one step in the healing process; skilled communication, patient education, engagement, and partnership are required for successful treatment of chronic diseases.

The patient was immune to hepatitises A and B. After a multidisciplinary discussion with neurology, pulmonary, and the internal medicine teams, the patient was started on high-dose steroids for neurosarcoidosis. Steroids were weaned slowly, and the patient was transitioned to methotrexate and infliximab.[3] One and a half years after the diagnosis, repeat MRI of the spine revealed near-complete resolution of the mass and surrounding edema (Fig. 3). The patient is back to biking the trails of the Sierra Nevada.

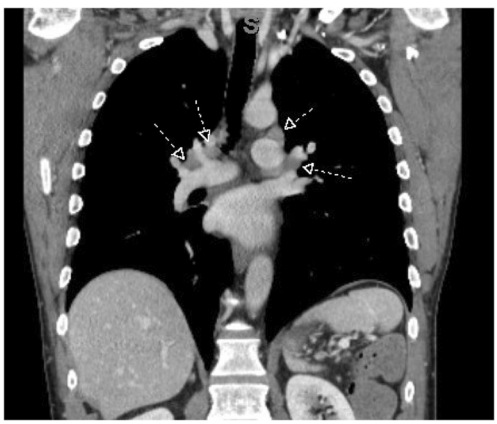

Figure 2 Computed tomography (CT) of the chest showing bilateral hilar lymphadenopathy, left greater than right.

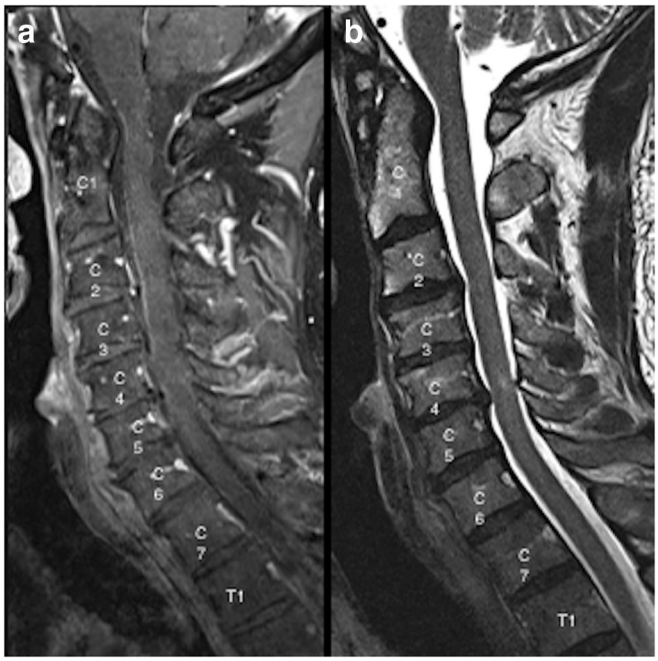

Figure 3 Magnetic resonance imaging (MRI) images of the cervical spine showing sagittal views of a largely resolved cervical cord mass. T1-weighted, gadolinium-enhanced (panel a) and T2-weighted (panel b) images of the cervical spine were taken approximately 1.5 years after treatment.

DISCUSSION

"Slowing down when you should" refers to the critical juncture when clinicians recognize that initial diagnostic considerations do not adequately explain a patient's presentation, prompting additional investigation.[4,5] This juncture marks a transition from automated and intuitive thinking (system I), to analytical and cognitively laborious thinking (system II). Through deliberate practice, clinicians develop situational awareness and background knowledge to carefully monitor for clues that warrant re-framing patients and systematically re-considering their differential.[4,5]

In this case, the discussant's initial thinking was automatic: she used pattern recognition to note "stocking-glove" distribution of symptoms, activating her illness scripts for length-dependent peripheral polyneuropathies. However, by noting mismatches between the patient's symptoms (involvement of hands prior to feet; ulnar pattern of involvement, rapid progression; bowel and bladder dysfunction) and her illness scripts for length-dependent peripheral polyneuropathy, she "slowed down," and was ultimately able to localize the lesion to the cervical spinal cord. In this analytic mode, she activated a series of diagnostic schema throughout the case, eventually honing in on the correct diagnosis.

Although the value of "slowing down when you should" was included as a top ten core concept of modern clinical reasoning theory, helping trainees build this skill can be challenging.[6] The "diagnostic time-out" is one way to teach trainees to consciously "slow down" to prevent diagnostic errors.[7] With time and space created for reflection, trainees consider a series of questions to check their diagnostic impressions. Additional work is needed to study the impact of diagnostic time-outs, but, in the face of limited data, this pause can serve as an accessible teaching tool.

As suggested in the discussant's comments, this patient's diagnosis was made possible through multidisciplinary discussions and collaboration between multiple teams. Hollywood depicts diagnosis as a process requiring the genius of just one physician; however, in reality, teams of providers and patients are needed to rapidly get to the bottom of complex cases. In fact, the Academy of Medicine's report *Improving Diagnosis in Healthcare* highlighted the need for improvements in collaboration in the realm of diagnosis. Humility and the drive for collaboration in diagnosis are markers of expertise and should be encouraged in trainees and experienced clinicians alike.

CLINICAL TEACHING POINTS

1. Sarcoidosis is a rare, chronic, multi-organ disease of unknown etiology that affects people worldwide of all ages and is characterized by tissue infiltration by non-caseating granulomas.[8]
2. Virtually any organ system can be involved by sarcoidosis. The lymphatic, respiratory, and nervous systems are often impacted.[8]
3. CNS sarcoidosis or neurosarcoidosis can have wide-ranging presentations including involvement of the central and peripheral nervous system.[3,9]
4. Neurosarcoidosis presenting as a spinal cord mass lesion is rare, but should be considered in the differential diagnosis of spinal cord lesions, along with malignancy.[10]

5. When biopsy of neural tissue is of high risk, biopsy of non-neural tissue should be prioritized to support a diagnosis of probable neurosarcoidosis.[3]

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Compliance with Ethical Standards:

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