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Clinical Reasoning: A 40-Year-Old Woman Presenting With Encephalopathy and Paraparesis

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Abstract:

Patients with acute to subacute multifocal neurological abnormalities often have a unique presentation, and their diagnosis and management can be challenging. We present the case of a 40-year-old patient who presented with a four-day history of confusion, bradyphrenia, right facial droop, bilateral lower limb weakness, urinary incontinence, and hypothermia. This case highlights the diagnostic approach to patients with subacute multifocal neurological abnormalities, the importance of considering coexisting systemic illnesses in the diagnosis, and their management. Readers will explore the diagnostic steps our group has considered to reach our final diagnosis and the importance of management for our leading diagnosis.

Section 1

A 40-year-old previously healthy woman with no past medical or neurological history presented to the emergency department after sustaining a fall. There was a four-day history of confusion, bilateral lower limb weakness, and urinary incontinence. There was no history of back pain or trauma. She was hypothermic (34.6 degrees Celsius), her heart rate was 100 beats per minute, and she had normal blood pressure and oxygen saturation. On physical exam, she had a dry hyperpigmented rash over her shins, back and buttocks. There was no evidence of active arthritis or facial rash. She was noted to have urinary retention. Her neck was supple, and she had a normal respiratory, cardiovascular, and abdominal examination.

On the mental status exam, she was alert but bradyphrenic, oriented only to person with a digit span of four. Cranial nerves exam was normal except for asymmetrical right-sided facial weakness, sparing the forehead. Motor examination showed bilateral lower limb weakness (from 1/5 for bilateral hip extension to 4-/5 for bilateral plantar flexion), hypotonia and absent deep tendon reflexes. Despite the confusion, our patient could participate in a sensory exam which failed to elicit a sensory level to pinprick, and crude joint position sense was intact.

Questions for consideration

1. Where is the lesion?
2. What is your differential diagnosis?
3. What should be the next steps in the diagnostic process?

Section 2

Due to bilateral lower limb weakness, urinary retention, and autonomic dysfunction, we initially localized this patient's pathology to the central nervous system (CNS), and most likely predominantly involving the spinal cord. We localized her lesion to the thoracolumbosacral level since the upper limbs were intact. The deficits involved the lateral corticospinal and

descending autonomic tracts to the sacral centre for bladder control, sparing the lateral spinothalamic tract and dorsal columns. The encephalopathy was hypothesized to be due to the hypothermia itself or bilateral diffuse cortical dysfunction from an infectious, inflammatory, or metabolic process, and the hypotonia due to spinal shock. The upper motor neuron facial weakness hinted at possible subcortical or bulbar involvement.

Infectious encephalitis with transverse myelitis was the main differential. There was no history of vitamin deficiencies, malnutrition nor heavy alcohol abuse to support a Wernicke's encephalopathy. The subacute progression made a vascular event unlikely. Also, in the absence of a personal or family history of cancer or B symptoms, a neoplastic process was initially lower on the differential.

We obtained a complete blood count and coagulation study (both were within normal limits), and a lumbar puncture (LP) was performed. The cerebrospinal fluid (CSF) analysis showed a white blood cells (WBC) count of 109 x 106/L (normal = 0-5 x 106/L) that were polynucleated (95% neutrophils), a red blood cells (RBC) count of 147 x 106/L (normal = none), a protein concentration of 3.22 g/L (normal = 0.15-0.55 g/L), and a glucose concentration of 0.8 mmol/L (normal = 2.2-3.9 mmol/L). Antimicrobials were started hastily covering for Mycoplasma pneumoniae, listeria, meningococcal meningitis, and Streptococcus pneumoniae. We sent meningitis multiplex testing on CSF (Biofire M/E), that included E. coli, Haemophilus influenzae, Listeria, Neisseria, Streptococcus agalactia (Group B), Streptococcus pneumoniae, Cytomegalovirus, antivirus, HSV-1, HSV-2, HHV-6, Parechovirus, VZV, and cryptococcus. We also tested for Mycoplasma with serum titers (IgM) and Biofire nasopharyngeal swab (PCR). CSF Mycoplasma PCR was not pursued given the clinical evolution and presentation (e.g., lack of respiratory symptoms), and the literature review indicating that CSF PCR testing lacks sensitivity. [1] All results returned negative.

Because of low CSF glucose, we wanted to rule out neurosarcoidosis, tuberculosis (TB) and leptomeningeal carcinomatosis. CSF cytopathology, TB cultures, a positron emission tomography (PET) scan, and a computed tomography (CT) scan of the chest, abdomen, and pelvis were performed and were negative for granulomatous disease and malignancy.

A magnetic resonance imaging (MRI) of the entire neuraxis was done without gadolinium because she had an acute kidney injury (infectious/inflammatory versus obstructive uropathy with secondary acute kidney injury). The brain MRI revealed extensive abnormal areas of T2 hyperintense signal in the dorsal medial right thalamus, with bilateral patchy hypothalamic involvement, also involving the anterolateral pons bilaterally and the tegmentum, scattered foci in the medulla, scattered foci in the cerebellum hemispheres, and diffusion signal in the centrum semiovale, corona radiata and internal capsule bilaterally. The spine MRI revealed diffuse myelopathy beginning at T3-4 and extending to the tip of the conus medullaris; the signal abnormality was predominantly central, including grey and white matter involvement. (Figure 1)

Given the above results:

1. Can you narrow down the differential diagnosis?

2. What additional tests do you want to order?

Section 3

Given the abnormal signal changes on MRI that involved the hypothalamus, thalamus, periependymal surface of the fourth ventricle, and dorsal medulla, in addition to the longitudinally extensive transverse myelitis (LETM), we suspected Neuromyelitis Optica Spectrum Disorder (NMOSD). However, the robust inflammatory CSF results raised some doubts about NMOSD. Her CSF showed neutrophilic pleocytosis, which is uncommon with NMOSD, but previously demonstrated to be associated with AQP4-antibody positive NMOSD. [2] Therefore, we extended the differential to include autoimmune/neuro-inflammatory diseases (Systemic Lupus Erythematosus (SLE) related myelitis and Sjogren's Syndrome).

With careful consideration, she was given high-dose methylprednisolone (1g/day IV) for five days. After the renal function normalized, a contract enhanced (C+) MRI of the orbits was performed and showed no evidence of optic neuropathy/neuritis. On the second day of hospitalization and day 1 of methylprednisolone, the patient developed hemolytic anemia that was initially considered drug-induced due to Ceftriaxone or autoimmune.

We sent an extensive rheumatological workup given the rash and the possible autoimmune hemolytic anemia. She was found to have low complements (C3 = 31 mg/dL, normal = 80-190 mg/dL; C4 < 2 mg/dL, normal = 10-50 mg/dL), high antinuclear antibodies (ANA) (1:640 IU/mL, homogenous cytoplasmic) and anti-double stranded DNA (>800; ≥100 is positive). Our patient fulfilled SLE criteria by having dermatologic involvement, hemolytic anemia, CNS symptoms, and positive serum antibodies. [3] Given the severity of her deficits, we started plasmapheresis (PLEX) (six sessions in total).

Repeat LP ten days after her initial presentation to assess for residual inflammation showed normalization of her CSF parameters, which can be observed with transverse myelitis associated with SLE. [4] Rituximab was started as maintenance therapy, anticipating she would test positive for NMOSD, as the two autoimmune diseases can coexist. [5] Her serum anti-Myelin Oligodendrocyte Glycoprotein (MOG) and anti-Aquaporin 4 (AQP4) antibodies sent before we started PLEX returned negative.

She was hospitalized for one month, improved significantly, was discharged to neuro-rehab, and could walk two months after her initial presentation. A repeat MRI without contrast of her neuraxis ten months and nineteen days after her initial MRI entirely normalized. There were no new signal abnormalities in the brain and cervical spinal cord. (Figure 2)

Discussion

Our patient was diagnosed with seronegative NMOSD and Systemic lupus erythematosus (SLE). SLE is an autoimmune condition which can have neuropsychiatric manifestations, stroke, seizures, and peripheral neuropathy. [3] Myelopathy is a CNS manifestation seen in 1-3% of SLE patients. [4] One study found that the most common cerebral MRI finding in neuro-SLE was non-specific white matter hyperintensities followed by grey matter hyperintensities and brain atrophy. [6] Our patient's initial MRI was suspicious for NMOSD, a group of central nervous system inflammatory disorders characterized by severe, immune-mediated demyelination and axonal damage predominantly attacking the optic nerves and spinal cord. [7] This patient's

serum anti-AQP4 antibodies were negative, however anti-AQP4 antibodies can become positive years after disease onset; hence, it is important to continue serial serum samplings for AQP4 antibodies. [8]

Nevertheless, this patient meets the 2015 international panel for seronegative NMOSD because of core clinical characteristics (LETM and diencephalic clinical syndrome) and MRI brain T2 hyperintense lesions involving the diencephalon, dorsal medulla and periependymal brainstem lesions. [7] Several case reports show that SLE can coexist with NMOSD. One population study reported that 6.7% of SLE patients with neuropsychiatric symptoms tested positive for anti-AQP4 antibodies with myelitis. [9]

First-line treatment for SLE and NMOSD is identical, which involves high-dose steroids and plasma exchange. [5] The use of intravenous immunoglobulin (IVIG) in addition to high-dose intravenous steroids has also been shown to be superior to high-dose intravenous steroids alone [10, 11], but IVIG alone is not recommended. [11] However, while acute treatment for both diseases overlaps, long-term treatment and immunosuppression can differ. For instance, hydroxychloroquine is used in patients with SLE to reduce disease flares, but not in NMOSD. [5] Additionally, using steroid-sparing agents may be influenced by coexisting end-organ damage seen with SLE associated with NMOSD. For example, in patients with lupus nephritis without NMOSD, the drug of choice would be Cyclophosphamide or Mycophenolate Mofetil (MMF), but in patients with lupus nephritis with NMOSD, Cyclophosphamide has been shown to be ineffective. [12] Similarly, in patients diagnosed with NMOSD, frequently used immunosuppressants are Rituximab and Azathioprine [12], but using Rituximab for patients with SLE and lupus nephritis is controversial given that some studies failed to prove its superiority over placebo while others support its clinical effectiveness and safety. [13, 14] Interestingly, despite differences in long-term management, the prognosis for recovery of strength is similar for patients with combined SLE-transverse myelitis (TM) and NMOSD compared to SLE-TM alone with appropriate treatment. [15]

In summary, it is essential to consider the coexistence of SLE and NMOSD, as while acute treatment overlaps, long-term immunosuppression varies with the diagnosis. Specifically, it can

be extremely challenging to tease apart lupus myelitis from seronegative NMOSD, and the existence of end-organ involvement seen with SLE can affect the choice of immunosuppressants and overall prognosis.

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Figure 1: MRI (C-) brain and spine at initial presentation demonstrating extensive T2/FLAIR hyperintense lesions in the (A) midbrain, thalamus and juxtacortical region, (B) T2 longitudinally extensive transverse myelitis on spine, with (C) central cord involvement on axial sequences.

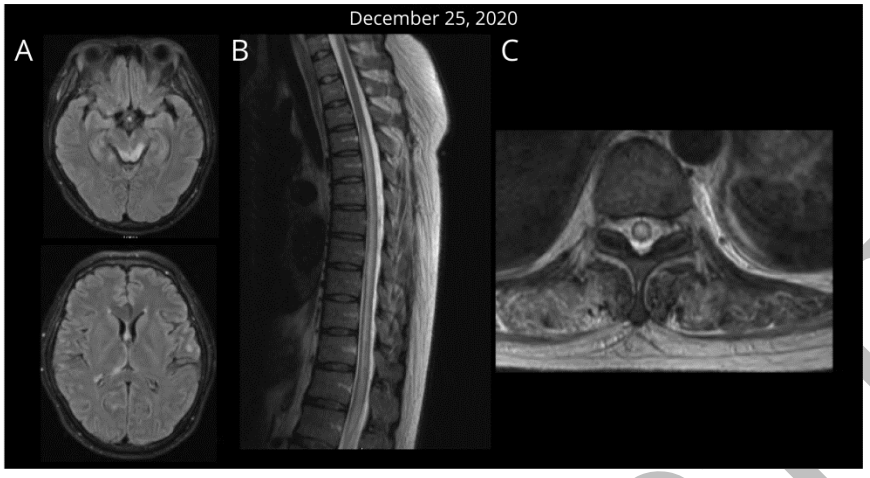
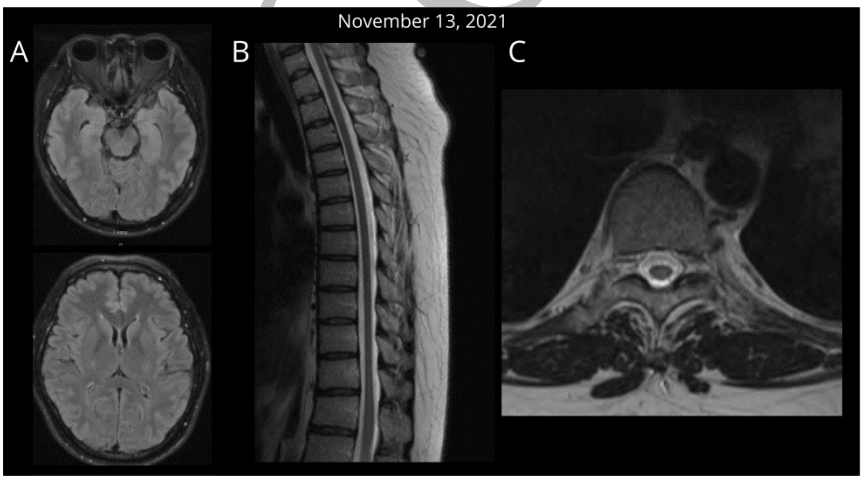


Figure 2: **MRI (C-) Full resolution of the diffuse inflammatory encephalomyelitis (LETM) in a repeat MRI (C-) 10 months and 19 days after initial presentation.** (Normal axial view of the brain (A), normal sagittal view of the spine (B), and normal axial view of the spine (C))



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