CLINICAL VIGNETTE

Demystifying a Demyelinating Disease: A Case Report of Tumefactive Multiple Sclerosis

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Case

A 68-year-old female with myelodysplastic syndrome (MDS) status was admitted from the Emergency Department with recurrent falls, headache, and left-sided numbness and weakness. Two weeks prior to admission, she noted increased difficulty maintaining her balance, particularly when turning towards her left side, and sustained multiple falls. She denied any prodromal symptoms, loss of consciousness, or head-strike with these falls. Several days later, she began experiencing left hand weakness and an inability to grasp or hold onto items in her left hand, followed soon after by difficulty walking even short distances due to progressive weakness in her left leg and foot. Past medical history includes allogeneic hematopoietic stem-cell transplant for MDS five years prior; complicated by graft-versus-host disease and chronic pancytopenia, treated with donor lymphocyte infusion.

Additional questioning after admission revealed daily morning headaches that improved throughout the day and were associated with posterior neck pain. She also reported two months of night sweats and a 30-pound weight loss, though denied fever or chills. Extended review of systems was otherwise negative. She denied chest pain, shortness of breath, dyspnea on exertion, vision changes, photophobia, rash, and joint pain or swelling.

On admission, the patient was hemodynamically stable with normal vital signs. She appeared chronically ill though in no acute distress. Physical exam was most notable for 4/5 strength and diminished sensation to light touch of the left upper and lower extremities. Her reflexes were 3+ in the bilateral upper extremities, 2+ patellar reflexes, and 0+ at the bilateral ankles. The remainder of her neurologic exam was normal, including strength and sensation of the right upper and lower extremities. Cardiopulmonary, abdominal, and skin exams were normal also unremarkable. Admission laboratory testing included white blood cell count of 4.96/µL, hemoglobin 11.1 g/dL, platelets 64,000/µL, sodium 132 mmol/L, and phosphorous 1.9 mg/dL. Neuroimaging was ordered including MRI brain and cervical, thoracic, and lumbar spine with and without contrast. MRI brain noted several regions of "ill-defined nodular, incomplete peripheral enhancement", with a 4.1 x 4.2 cm enhancing lesion in the right parietal lobe, 3.9 x 1.1 cm lesion in the right occipital lobe, and a 0.7 x 0.7 cm lesion in the left temporal stem, all with extensive vasogenic edema. MRI of the C/T/L spine demonstrated multifocal cervical and upper thoracic hyperintensities, most notably at C3-C4 with severe spinal canal narrowing and cord compression.

Differential diagnosis at this time included post-transplant lymphoproliferative disorder (PTLD), primary CNS lymphoma, demyelinating process, or atypical infection. Neurology, Neurosurgery, and Infectious Diseases were consulted. Lumbar puncture revealed clear, colorless CSF, with WBC 5/µL with lymphocytic predominance, RBC 1/µL, glucose 79 mg/dL, protein 54 mg/dL, negative CSF IgG and negative oligoclonal bands. Extensive CSF infectious studies, including EBV, CMV, Toxoplasmosis, HHV6, Cryptococcus, Histoplasma, Aspergillus, JC virus, and Karius testing were all unremarkable. CSF cytology was also negative.

Given unrevealing evaluation and progressive worsening of the neurologic exam, brain biopsy was planned after multidisciplinary discussion. Biopsy of the parietal lobe lesion was scheduled upon stabilization of the platelet count above 100,000/µL. Prior to the biopsy, her exam was notable for 5/5 strength in the right upper extremity, 2/5 strength in the left upper extremity, and 1/5 strength in the bilateral lower extremities with significantly diminished sensation to light touch of the left upper and lower extremities and new urinary retention requiring Foley catheter placement. Her platelet count improved with transfusion support and romiplostim injections, and she underwent successful stereotactic biopsy of right parietal lobe lesion.

Immediately following biopsy, the patient was started on pulse-dose steroids with methylprednisolone 1 g daily given her worsening symptoms and the pattern of enhancement on MRI most concerning for PTLD or a demyelinating process, with minimal improvement. Pathology eventually resulted with macrophage-rich lesions consistent with demyelinating disease of tumefactive multiple sclerosis. Given the incomplete response to high-dose steroids, a 5-day course of plasma exchange was initiated. Her exam improved with these therapies as well as aggressive physical therapy (PT) and occupational therapy (OT). Strength in the left upper extremity and right lower extremity improved to 3/5 with near-complete resolution of sensory deficits. MRI following completion of plasma exchange demonstrated interval improvement in the

size and degree of enhancement of the rim-enhancing lesions and vasogenic edema. She was discharged to an Acute Rehab Unit for ongoing high-intensity PT and OT and outpatient follow-up with neurology.

Discussion

Tumefactive multiple sclerosis (MS) is a rare variant of multiple sclerosis characterized by the presence of large, tumor-like lesions in the central nervous system (CNS). The annual incidence of tumefactive is estimated at 0.3 per 100,000 people, with prevalence of 1-3 per 1,000 MS cases.[1,2] Median age at onset is 37 years, with a female to male ratio of 1.2:1.[1] Unlike typical MS, where lesions are smaller and disseminated throughout the CNS, the demyelinating lesions of tumefactive MS are greater than 2 cm in size and are often associated with mass effect, edema, and ring enhancement.[1]

The clinical presentation of tumefactive MS is variable and atypical for demyelinating disease given the lesion size and potential for mass effect. Patients are usually polysymptomatic at initial presentation with simultaneous motor, sensory, cognitive, and/or cerebellar deficits.[1,2] Tumefactive lesions are also more likely than typical MS lesions to cause cortical deficits such as memory dysfunction, aphasia, and apraxia.[2] These characteristics, can make tumefactive MS difficult to distinguish from primary CNS neoplasms or abscesses, especially in patients without an established diagnosis of MS, which often leads to a delay in treatment. Cerebral biopsy is often required to confirm the diagnosis of tumefactive MS.[1,3]

As mentioned, tumefactive MS remains challenging to diagnose due to its rarity and ability to mimic primary CNS neoplasms, metastases, infarction, or atypical infections.[4] MRI is the best imaging modality for the diagnosis of tumefactive MS. The most frequently reported MRI feature is an open ring of enhancement with the incomplete portion of the ring abutting the gray matter of the cortex or basal ganglia, as seen in our patient, and are most commonly located in the frontal and parietal lobes (41-74% of lesions).[4] Cerebrospinal fluid (CSF) analysis is often pursued, though the results again are variable and can be normal or demonstrate a pleocytosis or elevated protein.[2] IgG oligoclonal bands, are considered the immunologic hallmark of MS and are positive in greater than 95% of patients with typical MS, but are found in only 52-70% of patients with tumefactive MS at initial presentation.[4,5] Common histopathologic findings of tumefactive demyelination resemble prototypic MS and reflect active inflammatory demyelinating disease. These include areas of demyelination with relative axonal sparing, foamy macrophages, reactive astrocytes, and perivascular lymphocytes.[4]

First-line treatment is typically with high-dose intravenous steroids (methylprednisolone 1 gram daily for 3-5 days) with the majority of patients (80%) having favorable response. Patients who do not improve significantly require escalation of therapy to plasma exchange.[2] In refractory cases, or in patients who continue to decline or relapse despite plasma exchange, combined regimen of monthly cyclophosphamide and biweekly rituximab plus oral steroids has been beneficial in case reports.[6,7]

Long-term prognosis in tumefactive MS is variable, with some patients experiencing a relapsing-remitting course similar to classical MS, while others experience a progressive disease course. In general, however, the clinical course of tumefactive MS tends to be more aggressive, with more rapid and severe progression of symptoms and greater than 1-year morbidity and mortality.[2] Patients with tumefactive MS have a longer time to diagnosis and initiation of treatment than typical MS. This case demonstrates many of the classic epidemiologic, clinical, and radiographical findings of tumefactive MS and underscores the importance of maintaining a high index of suspicion to minimize the need for brain biopsy and initiate appropriate treatment promptly.[3] Our patient's history of allogeneic stem-cell transplant further complicated her diagnosis, as the pattern of open rim-enhancement noted on MRI could also be seen in post-transplant lymphoproliferative disease. Further, patients who have previously undergone aHSCT are more prone to opportunistic infections, occurrence of secondary malignancies, and late-onset immune-mediated neurological sequalae such as central and peripheral immune-mediated demyelinating disease (CPID).[8]

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