DIAGNOSTIC & TREATMENT CHALLENGES OPEN ACCESS

"Will the Real Demyelinating Disorder Please Stand Up?"

From the National Multiple Sclerosis Society Case Conference Proceedings

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Abstract

A 46-year-old man presented with progressive painful monocular vision loss and left leg paresthesias. Workup demonstrated multifocal demyelinating lesions and CSF-restricted oligoclonal bands. He was diagnosed with multiple sclerosis (MS), but follow-up testing was notable for positive myelin oligodendrocyte glycoprotein–immunoglobulin G (MOG-IgG). We discuss implications and clinical considerations for MOG-IgG positivity in MS.

Case Report

A 46-year-old White man presented with 2 weeks of progressive left-sided vision loss with associated pain with extraocular movement (EOM), headache, and photophobia. He further reported several weeks of circumferential numbness and tingling in his distal left lower extremity (LLE). He did not have any bowel or bladder dysfunction and denied any sensory symptoms along the torso. He denied any preceding trauma, surgery, vaccination, or infection. He had never had an event like this before. His medical history was notable for hypertension, hyperlipidemia, and tobacco use disorder, and he had no personal or family history of autoimmune disease.

His general examination was unremarkable with normal vital, cardiopulmonary, and skin examinations. His ophthalmologic examination revealed poor visual acuity (VA) on the left with only the ability to count fingers (CF) at 3 feet and normal high contrast VA on the right. He also had pain with EOM testing and positive afferent pupillary defect in the left eye but no evidence of optic disc edema or pallor and normal-appearing vessels on fundoscopic examination. Neurologic examination was notable for symmetrically brisk 3+ patellar reflexes with crossed adductors and moderately decreased vibratory sense at the left great toe but otherwise intact cranial nerve (other than optic findings), motor, coordination, and gait assessments.

He was admitted to the inpatient neurology service for further diagnostic evaluation and management. MRI of orbits revealed abnormal T2 signal and contrast enhancement of the intraorbital segment of the left optic nerve with optic nerve sheath involvement compatible with optic neuritis/perineuritis (Figure 1). MRI brain revealed T2/fluid-attenuated inversion recovery hyperintense periventricular and subcortical white matter lesions, some of which had contrast enhancement (Figure 2). Subsequent MRI cervical spine and thoracic spine also revealed multiple areas consistent with active demyelination (Figures 3 and 4). Laboratory results including comprehensive metabolic panel, complete blood count, inflammatory markers (erythrocyte sedimentation rate and C-reactive protein), and Lyme antibody testing were unremarkable. Inpatient optical coherence tomography (OCT) revealed normal retinal nerve fiber layer thickness bilaterally (84 μm in the right eye and 86 μm in the left eye), but the ganglion cell inner plexus layer was mildly thinned in the left eye (71 μm) compared with the right eye (75 μm).

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Glossary

AQP-4 = aquaporin-4; **CF** = count fingers; **DMT** = disease-modifying therapy; **EOMs** = extraocular movements; **IVMP** = IV methylprednisolone; **LLE** = left lower extremity; **MOGAD** = MOG antibody–associated disease; **MOG-IgG** = myelin oligodendrocyte glycoprotein–immunoglobulin G; **MS** = multiple sclerosis; **NMOSD** = neuromyelitis optica spectrum disorder; **OCBs** = oligoclonal bands; **OCT** = optical coherence tomography; **RMS** = relapsing MS; **VA** = visual acuity.

He was diagnosed with MS based on fulfilling 2017 McDonald criteria with dissemination in space from spinal cord and periventricular lesions and dissemination in time with the presence of both active and chronic lesions in the brain and spinal cord. Lumbar puncture was deferred, and several laboratory results were still pending before discharge. He was treated with 5 days of IV methylprednisolone (IVMP) with improvement of VA CF to 20/50 (high contrast) and discharged with a plan to establish care in the MS Center. After discharge, serum myelin oligodendrocyte glycoprotein–immunoglobulin G (MOG-IgG) (live cell-based assay) resulted as positive with a clear positive titer of 1:100. His aquaporin-4 (AQP-4) Ab testing was negative.

At follow-up visit 2 weeks later, he reported persistent left foot numbness (improved from previous involvement of distal LLE). His visual acuity in the left eye had improved remarkably from VA CF (at initial presentation) to 20/25. However, his given diagnosis of MS was brought into question because of certain clinical and imaging features along with the MOG-IgG positivity. Additional laboratory testing and lumbar puncture were recommended for further evaluation. Serologic testing including thyroid studies, vitamin B12, methylmalonic acid, copper, ceruloplasmin, and zinc was within normal limits, and anti-nuclear antibody was negative. Lumbar puncture was completed with normal cell count, protein, glucose, and IgG index, but there was evidence of CSF-restricted oligoclonal bands (OCBs) with type 2 banding pattern.

After careful consideration of the available data, it was determined that he had a diagnosis of MS rather than MOG antibody–associated disease (MOGAD). Relevant factors guiding this determination included his overall clinical presentation and OCB positivity. Initiation of disease-modifying therapy (DMT) was recommended, but the patient declined initiating treatment.

The patient re-presented a year later with subacute onset of vertigo, unsteadiness, and heat sensitivity. His examination demonstrated mild difficulty with EOM (elicited vertiginous symptoms) and impairment in tandem gait. Repeat MRI demonstrated a new, contrast-enhancing right medullary lesion. He was treated with another course of IVMP and agreed to start long-term immunotherapy consisting of ocrelizumab. Repeat anti-MOG IgG testing demonstrated the same titer results of 1:100. Follow-up OCT revealed severe thinning (<1st percentile of normal controls) in the retinal nerve fiber layer (62 μm) and ganglion cell inner plexus layer (55 μm) of the left eye.

Differential Diagnostic Considerations

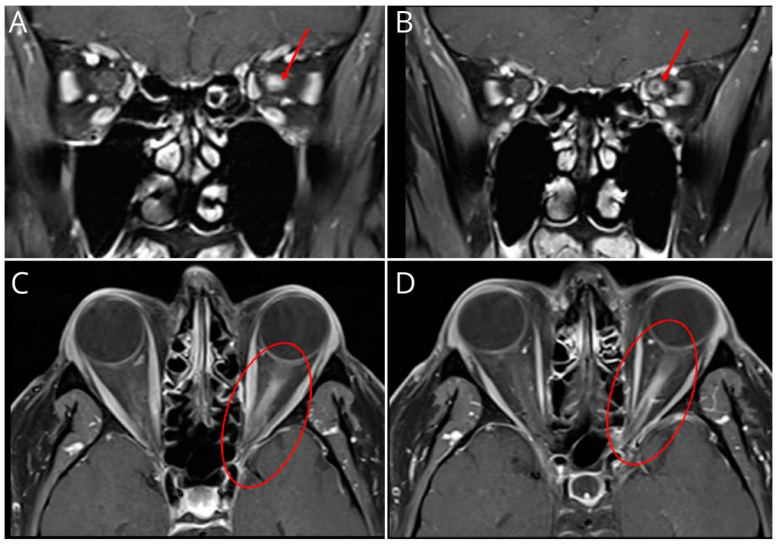
For the case in question, one may consider either relapsing MS (RMS) or MOGAD as the 2 top differential diagnoses. His presentation with multifocal inflammatory activity, chronic and active demyelinating lesions in the brain and spinal cord, relatively bland CSF along with CSF-restricted OCBs would support a diagnosis of RMS. However, features atypical for MS included the severity of his vision loss with ON, extensive optic nerve enhancement with perineural involvement, robust and remarkable response to steroids, and presence of MOG-IgG with a clear positive titer (≥1:100), all of which could suggest the alternate diagnosis of MOGAD. MRI findings with few, poorly demarcated intracranial lesions also support a diagnosis of MOGAD, although the short-segment cord lesions are more suggestive of RMS.[1] Although not observed in this particular case, the presence of a central vein sign would also more strongly suggest a diagnosis of MS rather than MOGAD.[1] In addition, OCT with severe optic nerve thinning may be seen more commonly with optic neuritis from MOGAD as opposed to RMS.

Neuromyelitis optica spectrum disorder (NMOSD) is another neuroinflammatory condition characterized by optic neuritis and spinal cord lesions. AQP-4 Ab-associated NMOSD was ruled out in this case by the negative AQP-4 Ab testing. Although seronegative NMOSD could be considered, this was excluded in this case because of the overall clinicoradiologic syndrome and presence of persistently positive MOG-IgG.

Infectious processes that may present with optic neuritis and spinal cord lesions such as mycoplasma, syphilis, varicella zoster virus, HIV, human T-lymphotropic virus (HTLV), or others should be considered and tested for accordingly as guided by clinical presentation. Para/postinfectious presentations such as acute disseminating encephalomyelitis after a viral illness may also be considered. He denied any preceding or associated infectious symptoms and lacked other findings to suggest these diagnoses.

Other inflammatory or rheumatologic disorders such as sarcoidosis, Bechet disease, and vasculitides may cause an optic neuritis with intracranial and/or spinal cord lesions. However, these were believed to be less likely in this case because of lack of other associated symptoms, imaging features, and negative rheumatologic testing thus far.

Figure 1 Orbital MRI Revealing Left Optic Neuritis and Perineuritis



Coronal T1 postcontrast images of orbits revealing contrast enhancement of the left optic nerve (A) and perineural sheath (B). Axial T1 postcontrast MRI orbit images with contrast enhancement of the prechiasmatic left optic nerve (C) with extension to the perineural sheath (D).

Finally, neoplastic processes related to solid tumors or lymphoma should be considered on the differential especially in an individual with a history of smoking. Again, his lack of systemic symptoms, normal laboratory findings otherwise, and overall benign clinical course made these lower on the differential.

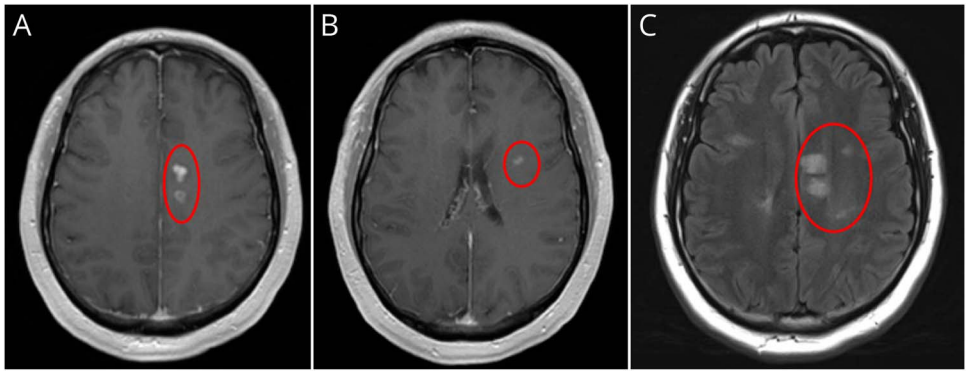
Final Diagnostic Consideration and Treatment Plan

Given the fulfillment of McDonald criteria, CSF-restricted OCB positivity, and lack of anterior optic nerve involvement along with intracranial and short-segment spinal cord findings, his presentation was believed to be more representative of RMS as opposed to MOGAD. He was initiated on a B-cell–depleting therapy because this has been shown to be an effective mechanism in reducing relapses in MOGAD and as a DMT in MS.[2,3] At a follow-up visit 2 years from initial presentation, he has been overall stable since initiating B-cell–depleting therapy with no evidence of relapse or new lesion formation.

Discussion

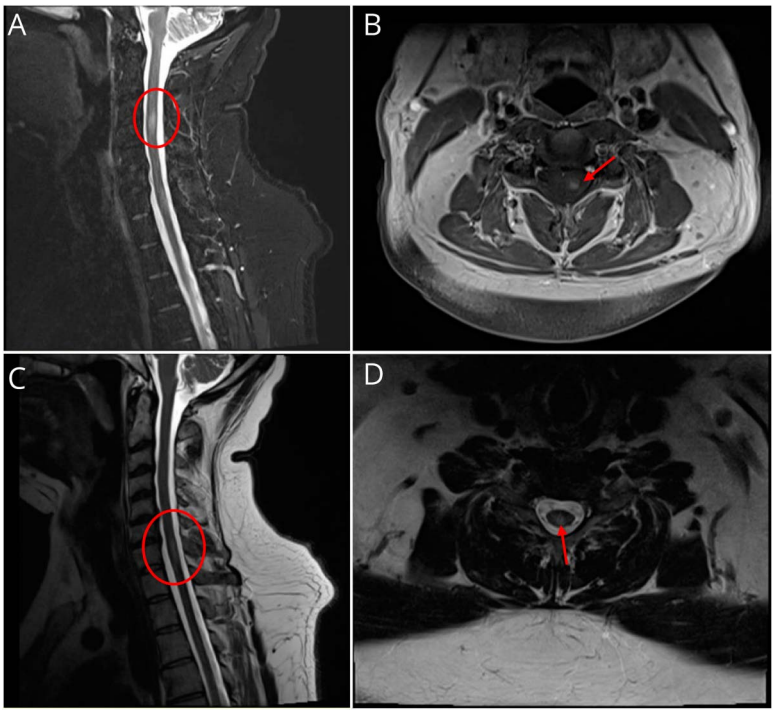
With the emerging knowledge surrounding MS-related disorders and mimics, extensive serologic testing is often completed before an MS diagnosis to ensure that "no better explanation" exists. Among this testing, MOG antibody assessment is often completed because MOGAD can appear similar to MS but may require different treatment considerations. Rates of MOG-IgG positivity in MS cohorts has been reported to be very low, with one study noting that 0.29% of patients with MS tested positive for MOG antibody (with a clear positive titer of >1:100), while others report it to be seemingly rare or absent in their cohorts.[4,5] However, in

Figure 2 Brain Imaging Revealing Demyelinating Lesions



Axial MRI brain T1 postcontrast (A and B) and T2/FLAIR (C) sequences with subcortical and periventricular white matter lesions, some of which appear poorly demarcated. FLAIR = fluid-attenuated inversion recovery.

Figure 3 Cervical Spinal Cord Imaging With Evidence of Demyelination



A short-segment hyperintense lesion at C3-C4 spinal level seen on the sagittal T2 short tau inversion recovery (STIR) sequence (A) with associated T1 postcontrast enhancement on axial view (B) appears typical for active demyelination. Another short-segment hyperintense lesion at C7 spinal level seen most clearly on sagittal T2 (C) and axial T2 (D) views also appears consistent with demyelination.

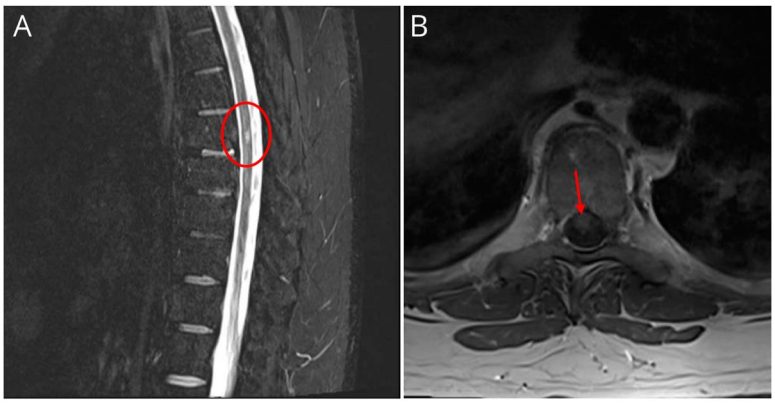
clinical practice, this situation is becoming increasingly common with increased testing for MOG-IgG antibody in patients who present with initial demyelinating events.

OCB positivity is also infrequent in MOG-IgG–positive patients but can be seen in 10%–20% of MOG-IgG–positive patients, sometimes being transiently present.[6,7] Furthermore, recent MOGAD diagnostic consensus criteria indicate that presence of low-titer MOG (defined as 1:10 to <1:100 on cell-based assay) and OCB positivity are "red flags" for MOGAD because "low-titer" MOG positivity can be seen in MS and other disorders.[8]

Dual positivity for MOG-IgG and OCBs may represent a diagnostic and management conundrum because of uncertainty of clinical diagnosis. While they are more precise in most of the cases, current diagnostic criteria are not always accurate in differentiating MS cases from MOGAD cases especially in those with clear positive MOG-IgG titers.[9] Furthermore, it is becoming increasingly recognized that overlapping characteristics may be seen in CNS demyelinating disorders such as MS and MOGAD, further clouding diagnostic certainty.[3]

Recent studies have looked at potential clinical implications for OCB and MOG-IgG dual positivity. OCB positivity in

Figure 4 Thoracic Spinal Cord Imaging With Presence of Active Demyelination



Sagittal T2 STIR short-segment hyperintense lesion at T7 spinal level (A) and axial postcontrast imaging of T7 spinal cord lesion with contrast enhancement (B) are also indicative of active demyelination. STIR = short tau inversion recovery.

MOGAD has been associated with higher risk of relapse.[10] Dual MOG-IgG/OCB positivity has been reported to have higher MRI lesion burden and more commonly "polyfocal" clinical presentations.[11] Given this information, the patient in our case would fall into the realm of dual MOG/OCB positivity and had a clinical presentation consistent with initial polyfocal clinical presentation and relapse within a year.

For the time being, there is no clear consensus in the field on how to manage patients with MOG positivity in MS or dual MOG/OCB positivity. Patients with these findings may often be labeled as MS because of OCB positivity, but management considerations may differ because of potentially different clinical course as outlined above. Based on currently available data, it may be prudent to consider higher efficacy therapy in MOG-IgG–positive MS or dual MOG/OCB-positive patients because of risk of relapse, higher MRI lesion burden, and polyfocal presentation. In this subset of patients, providers may consider using therapies commonly used to treat MS and MOGAD, such as B-cell–depleting agents.[3] However, the final decision should always rely on clinical presentation and shared decision making between the patient and provider.

Author Contributions

A. Elfasi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. M.D. Goldman: drafting/revision of the manuscript for content, including medical writing for content. C. Riley: drafting/revision of the manuscript for content, including medical writing for content. S.S. Zamvil: drafting/revision of the manuscript for content, including medical writing for content. S.D. Newsome: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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