Abstract

A woman presented at age 18 years with partial myelitis and diplopia and experienced multiple subsequent relapses. Her MRI demonstrated T2 abnormalities characteristic of multiple sclerosis (MS) (white matter ovoid lesions and Dawson fingers), and CSF demonstrated an elevated IgG index and oligoclonal bands restricted to the CSF. Diagnosed with clinically definite relapsing-remitting MS, she was treated with various MS disease-modifying therapies and eventually began experiencing secondary progression. At age 57 years, she developed an acute longitudinally extensive transverse myelitis and was found to have AQP4 antibodies by cell-based assay. Our analysis of the clinical course, radiographic findings, molecular diagnostic methods, and treatment response characteristics support the hypothesis that our patient most likely had 2 CNS inflammatory disorders: MS, which manifested as a teenager, and neuromyelitis optica spectrum disorder, which evolved in her sixth decade of life. This case emphasizes a key principle in neurology practice, which is to reconsider whether the original working diagnosis remains tenable, especially when confronted with evidence (clinical and/or paraclinical) that raises the possibility of a distinctively different disorder.
Case Presentation

The patient is a 57-year-old woman followed at our comprehensive multiple sclerosis (MS) center at the Cleveland Clinic after decades with the diagnosis of clinically definite, relapsing-remitting MS (RRMS), followed by a transition to secondary progressive MS (SPMS), who now presents with longitudinally extensive transverse myelitis. The inception of this patient’s neurologic course began in 1981 at age 18 years with partial transverse myelitis, followed by an episode of double vision (Figure 1). Following corticosteroid therapy, she recovered completely from both syndromes, and a diagnosis of clinically definite RRMS was established. She was later treated with interferon beta-1a and remained neurologically stable on this therapy for nearly 3 decades until 2009 at which time a new clinical relapse prompted the transition of her disease-modifying therapy (DMT) to glatiramer acetate (Figure 1).

Although she remained stable on glatiramer acetate with no evidence of disease activity for approximately 10 years, a follow-up visit in May 2019 revealed worsening on tests of processing speed, timed 25-foot walk, and fatigue. A surveillance brain MRI at that time showed lesions highly characteristic for MS (ovoids, Dawson fingers, periventricular plaques, and lesions perpendicular to the long axis of the ventricles) and multiple new and/or enlarging T2 hyperintense nonenhancing lesions in the deep white matter when compared with a February 2017 scan (Figure 2). Her course at that time was most consistent with SPMS.

In November of the same year, the patient developed the subacute onset of bilateral lower extremity weakness, rendering her nonambulatory and requiring the use of a wheelchair (Expanded Disability Status Scale score of 7). Examination at that time revealed full strength in the upper extremities, decreased strength in the lower extremities (rated 3 on the Medical Research Council scale), diminished sensation to vibration that was worse on the left vs the right lower extremity, diffusely brisk reflexes without clonus, and finger-to-nose dysmetria. Following high-dose oral prednisone treatment, she once again exhibited significant improvement and was able to ambulate with a walker. By February 2020, the patient was transitioned to siponimod, an oral sphingosine-1-phosphate (S-1-P) receptor modulator.

Figure 1 Chronological Heat Map

In this figure, we detail the condition of the patient over time. The longitudinal axis (left to right) depicts the condition of the disease, whereas the smaller amplitude and lighter color indicates greater stability of the disease. Alternately, the expanded amplitude of the colored heat map (above and below the horizontal linear axis over time) designates increased disease activity (whether on a clinical or paraclinical basis) or complications of the treatment of disease. Other fields of information are added either above or below the heat map and include information about treatments, diagnoses, commentaries adding contextual perspectives, and results from specific test assessments from each most relevant period of clinical decision making. Each field is consistently color coded throughout as defined in the figure legend.16

Glossary

DMT = disease-modifying therapy; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder; RRMS = relapsing-remitting MS; S-1-P = sphingosine-1-phosphate; SPMS = secondary progressive MS; UTI = urinary tract infection.
One month following the transition to siponimod, she reported difficulty ambulating, generalized weakness, dizziness, dysarthria, worsening spasticity, and confusion. Brain MRI showed greater than multiple new enhancing brain lesions, most prominently in the right centrum semiovale, anterior to the right lateral ventricle, and in the right superior periventricular region (Figure 3). She was treated with high-dose steroids and antibiotics for a concomitant urinary tract infection (UTI).

Two months later, she described the new onset of weakness in the left upper extremity, which was confirmed on examination, in conjunction with nonsustained ankle clonus bilaterally. Siponimod was held due to lymphopenia at 200 cells/μL.

She then presented to the emergency department with difficulty ambulating and altered mental status. A brain MRI showed no abnormal enhancements and no evidence of acute ischemia. MRI of the cervical and thoracic spine showed discontinuous short-segment (i.e., skip) nonenhancing lesions. She was treated with high-dose corticosteroids and antibiotics for yet another UTI, improved, and was subsequently discharged home. However, 1 week later, the patient was admitted to the hospital for worsening gait, dysphagia, and diffuse weakness. She was transferred to the intensive care unit, where she was intubated for airway protection and required vasopressors for blood pressure support. Imaging of the neuroaxis failed to demonstrate any interval changes. CSF analysis revealed an elevated IgG index and the presence of unmatched oligoclonal bands. Once the patient improved and stabilized, she was discharged to acute rehabilitation. While on the rehabilitation service, she developed severe weakness in the upper and lower extremities bilaterally that progressed to the point of exhibiting only trace movements in the upper extremities, paraplegia, and urinary retention.

Given the severity of deterioration, the patient was treated with IV methylprednisolone and a course of plasma exchange. Repeat imaging of the spinal cord now demonstrated a longitudinally extensive pattern of confluent hyperintensity with peripheral enhancement and marked edema that spanned from the cervicomedullary junction to the upper thoracic spinal cord (Figure 4). Serum testing by cell-based assay yielded a positive AQP4 IgG at a titer of 1:2,560, and a diagnosis of neuromyelitis optica spectrum disorder (NMOSD) was confirmed. Siponimod was discontinued while ocrelizumab, a CD20 monoclonal antibody, was initiated.

The patient currently has only trace movements in her lower extremities with limited antigravity movements in her upper extremities. She requires an indwelling Foley catheter and has significant spasticity.
Differential Diagnostic Considerations

This case raises 2 intriguing possibilities: The first is that our patient was originally misdiagnosed with RRMS and followed an atypical NMOSD course until she presented with cervicothoracic myelitis. An alternative hypothesis is that she developed 2 distinctive neuroinflammatory disorders in a temporal sequence, namely the onset of MS at 18 followed by the development of NMOSD at 57.

We will first discuss perhaps the more controversial hypothesis: the prospect that our patient’s presentation represented manifestations of NMOSD from the very start of her complex clinical course. This would render the original label of RRMS, the initial working diagnosis, as fundamentally incorrect. Based on the disease characteristics associated with the formulation of her working diagnosis, is there any evidence that an early misdiagnosis could have been avoided?

First, it is known that a minority of patients with NMOSD can, in fact, exhibit short-segment spinal cord lesions that are indistinguishable from the so-called classic skip lesions associated with MS.1 Furthermore, such patients may also have brain lesions that appear consistent with MS.2 Studies have shown that 60% of patients with NMOSD accumulate white matter lesions and that as many as 16% fulfill the Barkhof MRI criteria for MS.2,3

A misdiagnosis of MS could explain a lack of response to escalation of MS DMTs, while the patient’s previous stability on glatiramer may have been due to a protracted NMOSD remission, which can be a characteristic of the disorder.4 In addition, it is possible that our patient’s clinical deterioration was precipitated by the transition in DMT from glatiramer acetate to siponimod, as acute inflammatory activity associated with S-1-P modulator treatment has been documented in NMOSD.3,5,6

The alternate hypothesis for consideration is that the patient developed 2 distinct neuroinflammatory conditions occurring in a temporal sequence. Although her initial presentation of partial myelitis and a brainstem syndrome can occur in both MS and NMOSD, the near-complete recovery of such syndromes with corticosteroids is highly reminiscent of, albeit not specific for, MS. Our patient was well controlled without evidence of disease activity on interferon beta-1a for nearly 30 years. Subsequently, a new exacerbation prompted a transition in DMT to glatiramer acetate, which provided another decade of disease-free remission.

Radiographically, brain imaging studies revealed enhancing and nonenhancing brain lesions, with features highly characteristic for MS including ovoids, periventricular hyperintensities, Dawson fingers, and cerebral atrophy. Spinal cord imaging performed early in the disease course exhibited multifocal and discontinuous short-segment skip lesions, in keeping with the diagnostic criteria of definite MS.5 Furthermore, CSF oligoclonal bands (as present in our patient) are identified in ~85% of patients with MS, but in only ~15% of patients with NMOSD.3,5

The clinical course in our patient prior to 2019 included the documented transition from relapsing-remitting to SPMS. Development of progressive disability years after diagnostic confirmation and treatment of RRMS, is characteristic of SPMS, and is not an established feature of NMOSD.3,6 However, by mid-late 2019, our patient began to exhibit a marked escalation in both clinical and radiographic disease activity, including an episode of longitudinally extensive transverse myelitis (more than 30 years after the initial presentation), an observation that is highly atypical for MS.

Final Diagnostic Conclusions

Taken together with the highly characteristic lesions on brain imaging investigations (e.g., Dawson fingers, ovoids, periventricular lesions, and typical enhancements as demonstrated in both Figures 2 and 3), spinal cord skip lesions, and the absence of antecedent syndromes characteristic for and also part of the rigorous diagnostic criteria for NMOSD (e.g., longitudinally extensive myelitis, optic neuritis, area postrema
syndrome, or diencephalic syndrome), we believe that based on the evidence available, our patient’s initial disorder of CNS inflammation was more compatible with MS than with NMOSD. Her presentation at our center decades into her disease course, with a longitudinally extensive transverse myelitis and the presence of AQP4 antibodies, supports the development of yet a second neuroinflammatory disorder, NMOSD.

A study investigated a large cohort of patients with MS for the presence of aquaporin-4 antibodies in serum samples and found that the rate of misdiagnosis of NMOSD as MS was very rare, less than 1%. Unfortunately, testing for AQP4 antibodies was not available at the time of our patient’s initial presentation in 1981 and would not be widely available until some 25 years later.

**Discussion**

MS and NMOSD are separate diseases. MS is thought to result from an autoimmune attack targeting proteins expressed by myelin-producing oligodendrocytes. Alternately, NMOSD, a humoral autoimmune disease, was distinguished as a separate disease in 2004, with AQP4 identified as the target for the pathogenic antibody in 2005, long after the inception of our patient’s disorder in 1981 (Figure 1). Evidence is also now well established to genetically differentiate the predilection of these 2 disorders. Specifically, MS is associated with the HLA-DR2 (DRB1*1501) and typically presents early in life (from adolescence to middle age), whereas NMOSD has been shown to be associated with HLA-DR17 (DRB1*0301) and can present at any age.

There are highly salient and differentiating radiographic characteristics for MS and NMOSD and well-defined and evidence-based diagnostic criteria. However, it is important to note that patients with MS are at higher risk of developing other autoimmune disorders, making the possibility of 2 distinct neuroinflammatory disorders not untenable. For instance, it is clear that these 2 disorders can manifest in complex ways that raise diagnostic confusion, including the prospect that the 2 conditions might occur as separate entities in a temporally distinctive sequence. Although we cannot be certain, we believe that the analysis of the evidence available supports the contention that our patient did have RRMS, later transitioning into SPMS, and that she developed NMOSD in her sixth decade of life.

Our case report is instructive in that it emphasizes a crucial and salient principle in clinical practice. Specifically, the neurologist must remain vigilant and committed to periodically revisit a fundamental tenet in neurologic diagnosis: “does the ‘working diagnosis’ still work?” In our patient, answering the question with precision as to whether the working diagnosis of MS remained valid in the context of a potentially transformational clinical syndrome, longitudinally extensive transverse myelitis, required a well-codified, objective (now including the utilization of a highly sensitive and specific molecular diagnostic tool; the cell-based assay performed on serum for the identification of the AQP4 autoantibody), and a systematic surveillance plan for disease monitoring in conjunction with the interpretation of treatment response characteristics.

At least with respect to the new syndrome, the presence of the AQP4 antibody rendered the original diagnosis of MS no longer tenable, or that a second condition in the form of NMOSD, evolved in conjunction with, and temporally after the first (i.e., MS). Modification of the working diagnosis (es) was indeed tantamount so that an alternate and more appropriate treatment strategy could be formulated, one that provided potential efficacy for one and/or both conditions.

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the International Society of Neuroimmunology; he has served as a consultant and received honoraria from Biogen Idec, EMD-Serono, Genzyme, Novartis, Roche/Genentech, and Teva Pharmaceuticals, Inc., and has served or serves on Data Safety Monitoring Boards for Lilly, BioMS, Teva, and Opexa Therapeutics. Currently, S.S. Zamvil receives research grant support from the NIH, the NMSS, The Maisin Foundation, Biogen, and Celgene. E.M. Frohman serves on the Editorial Boards of Journal of Neurology, The Journal of the Neurological Sciences, and Neuroimmunology Reports; he has received speaker honoraria from Genzyme, Novartis, Janssen, and Alexion. T.C. Frohman serves on the Editorial Board of Neuroimmunology Reports; she has received speaker fees from Alexion. Go to Neurology.org/NN for full disclosure.

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Appendix Authors

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<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carolyn Goldschmidt, MD</td>
<td>Department of Neurology, Cleveland Clinic</td>
<td>Conception, manuscript drafting, clinical and imaging review, literature review, and critical revision of the manuscript</td>
</tr>
<tr>
<td>Steven L. Galetta, MD</td>
<td>Department of Neurology, New York University</td>
<td>Critical revision of the manuscript for intellectual content</td>
</tr>
<tr>
<td>Robert P. Lisak, MD</td>
<td>Department of Neurology, Wayne State University</td>
<td>Critical revision of the manuscript for intellectual content</td>
</tr>
<tr>
<td>Laura J. Balcer, MD, MSC</td>
<td>Department of Neurology, New York University</td>
<td>Critical revision of the manuscript for intellectual content</td>
</tr>
<tr>
<td>Andrew Hellman, PhD</td>
<td>Quest Diagnostics</td>
<td>Critical revision of the manuscript for intellectual content</td>
</tr>
<tr>
<td>Michael K. Racke, MD</td>
<td>Quest Diagnostics</td>
<td>Critical revision of the manuscript for intellectual content</td>
</tr>
<tr>
<td>Amy E. Lovett-Racke, PhD</td>
<td>Ohio State University</td>
<td>Critical revision of the manuscript for intellectual content</td>
</tr>
<tr>
<td>Roberto Cruz, MD</td>
<td>Department of Neurology, Doctors Hospital at Renaissance</td>
<td>Critical revision of the manuscript for intellectual content</td>
</tr>
<tr>
<td>Matthew S. Parsons, PhD</td>
<td>Emory University</td>
<td>Critical revision of the manuscript for intellectual content</td>
</tr>
<tr>
<td>Neda Sattarnezhad, MD</td>
<td>Department of Neurology, Stanford University School of Medicine</td>
<td>Critical revision of the manuscript for intellectual content</td>
</tr>
</tbody>
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<tr>
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<tbody>
<tr>
<td>Lawrence Steinman, MD</td>
<td>Department of Neurology, Stanford University School of Medicine</td>
<td>Critical revision of the manuscript for intellectual content</td>
</tr>
<tr>
<td>Scott S. Zamvil, MD, PhD</td>
<td>Department of Neurology, Program in Immunology, University of California at San Francisco</td>
<td>Conception and critical revision of the manuscript for intellectual content</td>
</tr>
<tr>
<td>Elliot M. Frohman, MD, PhD</td>
<td>Distinguished Senior Fellow (Sabbatical) Laboratory of Neuroimmunology of Professor Lawrence Steinman, Stanford University School of Medicine</td>
<td>Critical revision of the manuscript for intellectual content</td>
</tr>
<tr>
<td>Teresa C. Frohman, MPAS, PA-C</td>
<td>Distinguished Senior Fellow (Sabbatical) Laboratory of Neuroimmunology of Professor Lawrence Steinman, Stanford University School of Medicine</td>
<td>Critical revision of the manuscript for intellectual content</td>
</tr>
</tbody>
</table>

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