Clinical Reasoning: A 50-year-old woman with SLE and a tumefactive lesion

Jee-Hye Choi, BA
Asya Izraelit Wallach, MD
Dominique Rosales, MD
Stefan E. Margiewicz,
MD
H. Michael Belmont, MD
Claudia F. Lucchinetti,
MD
Mia T. Minen, MD,
MPH

Correspondence to
Dr. Minen:
minenmd@gmail.com

SECTION 1

A 50-year-old woman with a history of systemic lupus erythematosus (SLE) treated with methotrexate and hydroxychloroquine presented to the emergency department for evaluation of numbness and weakness of the left hand that began 12 hours earlier.

Twenty years ago, the patient had been diagnosed with SLE when she presented with Jaccoud arthropathy, nephritis, and bullous eruptions on the face, scalp, and trunk. Laboratory analysis at the time showed a positive antinuclear antibody with a speckled pattern and positive anti-dsDNA antibodies. Since her diagnosis of SLE, the patient had been hospitalized twice for suspected immune-mediated complications of the CNS.

On admission, the patient's initial examination revealed a left facial droop, left pronator drift, and decreased sensation to light touch in the distal left upper extremity. No lower extremity weakness or numbness was noted. Laboratory evaluation was remarkable for elevated erythrocyte sedimentation rate (40 mm/h), but normal levels of anti-dsDNA antibodies, C3, and C4. The brain MRI showed a new area of T2/fluid-attenuated inversion recovery

(FLAIR) hyperintensity within the subcortical white matter of the right posterior central gyrus and associated heterogeneous faint enhancement (figure 1, A–C). The spine MRI was normal. CSF analyses were performed, demonstrating glucose 51 mg/dL, protein 21 mg/dL, erythrocytes 0/mm³, leukocytes 0/mm³, and immunoglobulin G (IgG) index 2110, and negative oligoclonal bands, Gram stain, culture, venereal disease research laboratory, herpes simplex virus, *Borrelia burgdorferi*, and JC virus.

Over the course of the following 4 days, the patient's condition rapidly deteriorated. She developed worsening left-sided weakness, now including the left lower extremity, a left homonymous hemianopia, and dysarthria. Multiple brain MRIs over this time course showed markedly worsening signal abnormality throughout the right cerebral hemisphere involving multiple lobes (figure 1, D–F).

Question for consideration:

1. What is the differential diagnosis for a confluent enhancing juxtacortical/subcortical white matter lesion with T2/FLAIR hyperintensity on MRI as described in the above case?

GO TO SECTION 2

(A-C) Brain MRI on presentation including fluid-attenuated inversion recovery (FLAIR), T1 precontrast, and T1 postcontrast. (A) Axial FLAIR shows a large right hemispheric lesion in the precentral gyrus, with a smaller more anterior cortical hyperintensity. (B) Lesion appears heterogeneously hypointense on T1, with (C) faint contrast enhancement. (D-F) Repeat brain MRI acquired 3 days later. (D) Axial FLAIR, (E) T1 precontrast, and (F) postcontrast demonstrate progression of the same lesion 3 days later. (G-I) Brain MRI from patient's first presentation (5 years prior) of left hemiparesis and dysarthria, including FLAIR, diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC), demonstrates (J) FLAIR-hyperintense R posterior internal capsule and thalamus, with (K) DWI restriction and (L) faint dropout on ADC. (J-L) Brain MRI from patient's second presentation (4 years prior) including FLAIR, DWI, and ADC are consistent with area postrema syndrome: (J) FLAIR hyperintense lesion adjacent to the 4th ventricle, with (K) DWI restriction without (L) ADC dropout.

SECTION 2

Tumefactive demyelinating lesions (TDL) are defined as demyelinating lesions greater than 2 centimeters. They often appear on MRI as large T2-hyperintense brain lesions with contrast enhancement and varying degrees of mass effect.¹ TDLs are most commonly seen as a rare manifestation of multiple sclerosis (MS) but may also result from other primary demyelinating diseases (other MS variants such as Schilder disease, Marburg variant, and Balo concentric sclerosis, acute disseminated encephalomyelitis, and neuromyelitis optica spectrum disorder [NMOSD]), which may coexist with SLE,^{2,3} infection (particularly progressive multifocal leukoencephalopathy [PML]), genetic diseases¹ (leukodystrophies), and drug-induced conditions (methotrexate-induced leukoencephalopathy²). Other diagnoses that may radiologically mimic TDLs include nondemyelinating autoimmune diseases (IgG4-related disease⁴), malignancy (lymphoma, high-grade glioma, metastasis), and infarction.

Radiographically, tumefactive MS and tumefactive NMOSD look similar, and may have an incomplete ring of enhancement with the open side facing the cortex (which this case did not demonstrate) and involvement of the subcortical U fibers. PML also has a propensity for the subcortical U fibers, presenting as multifocal hyperintense FLAIR lesions, typically without significant mass effect or contrast enhancement, but there can be diffusion restriction. The imaging characteristics of methotrexate toxicity mirror that of PML. While lymphoma can heterogeneously enhance in immunocompromised patients, it more typically presents with a homogeneously enhancing mass or masses and is more typically located in the basal ganglia or periventricular white matter.

Questions for consideration:

1. How does the interval worsening of both the clinical and radiologic findings affect the differential diagnosis?
2. Which other studies should be performed as part of the workup?

GO TO SECTION 3

SECTION 3

After the initial MRI evaluation, the lesion was thought to be neoplasm or severe demyelination such as MS, NMOSD, or PML. Methotrexate-induced leukoencephalopathy was considered less likely since the patient only received low oral doses and the complication is more common in patients who receive methotrexate for a cancer indication. Given the increased risk of PML in patients with SLE compared to the general population, potentially due to immunosuppressive therapy or other disease factors,⁵ methotrexate was temporarily held. However, as subsequent imaging studies over the course of days revealed rapid progression of the disease, PML and neoplasm were considered less likely diagnoses.

Extensive bloodwork was performed. Anti-dsDNA was negative, anti-SS-A and anti-SS-B titers were elevated but at the patient's baseline, and the C3 and C4 levels remained roughly within normal ranges. The antiphospholipid panel and anti-rib-P

antibodies were also within normal ranges. HIV test was negative. Although other tests, including brain biopsy, were pending at this point, given that the patient's condition was rapidly deteriorating and infectious etiologies were determined to be less likely, the patient was treated with the following immunomodulatory therapies: high-dose IV methylprednisolone, IV immunoglobulin (IVIg), and 1 dose of cyclophosphamide.

The initial brain biopsy report demonstrated inflammation with prominent neutrophils and no evidence of malignancy or viral infection, but was inconclusive for any specific diagnosis. Several weeks later, the serum IgG neuromyelitis optica antibodies (anti-aquaporin-4) returned positive.

Questions for consideration:

1. How does anti-aquaporin-4 antibody (AQP4-Ab) help the diagnosis of NMOSD?
2. What are the histopathologic features of NMOSD?

GO TO SECTION 4

SECTION 4

With positive AQP4-Ab and symptomatic cerebral syndrome with a typical brain lesion, and exclusion of competing diagnoses, the patient was diagnosed with NMOSD.

The patient's biopsy sample was sent to Mayo Clinic for more specific analysis, which revealed AQP4 loss colocalized to regions with myelin-laden macrophages, pronounced glial fibrillary acid protein loss despite a fair amount of myelin preservation on proteolipid protein, scattered granulocytes (eosinophils and neutrophils) in non-necrotic regions, no evidence of Creutzfeldt cells, and vacuolated myelin consistent with myelin edema (figure 2). These pathologic findings are consistent with the pathologic diagnosis of NMOSD.⁶

The patient was treated acutely with 2 doses of rituximab, followed by maintenance dosing. Several weeks after receiving rituximab and weeks of inpatient rehabilitation, the patient regained strength but did not return to her baseline. At discharge, she had left inattention without neglect and residual left hemiplegia (persistent left facial droop, antigravity or better in all extremities).

DISCUSSION The discovery of the AQP4-Ab has streamlined the approach to diagnosis and increased our understanding of the pathogenesis of NMOSD. While optic neuritis and longitudinally extensive transverse myelitis remain the most common clinical manifestations of NMOSD, AQP4-Ab has been associated with a number of other syndromes involving the cerebrum, diencephalon, brainstem, and area postrema. To account for the spectrum of syndromes associated with AQP4 autoimmunity, neuromyelitis optica has been renamed NMOSD with an updated set of diagnostic criteria by the International Panel for NMO Diagnosis.⁷ According to the new criteria, NMOSD can be diagnosed with

positive AQP4-Ab and at least 1 of the 6 core clinical characteristics. Core clinical features include at least one of the following: optic neuritis, acute myelitis, unexplained hiccups or nausea with vomiting (area postrema syndrome), narcolepsy with typical diencephalic MRI lesions, or symptomatic cerebral syndrome with a typical MRI brain lesion. Without AQP4-Ab, the diagnosis requires at least 2 core clinical characteristics and other radiographic features.⁷ Thus, our patient's diagnosis of NMOSD is based on a positive AQP4-Ab and cerebral syndrome of hemiparesis and inattention.

As referenced in Section 1, this patient was previously hospitalized 5 years ago with acute onset progressive left hemiplegia, facial droop, and dysarthria, with elevated anti-dsDNA Ab (199 IU/mL), and imaging findings (figure 1, G–I) were interpreted as a subacute lacunar stroke, though given the similarity in imaging characteristics, it is also possible that this lesion represented a first subacute demyelinating attack. These symptoms nearly fully resolved within a month. A year later, she presented with a pressure-like headache associated with nausea, vomiting, and 2 weeks of dizziness; rheumatologic markers were normal at this time, but brain MRI demonstrated multiple T2/FLAIR hyperintense lesions, including one lesion (figure 1, J–L) adjacent to the fourth ventricle consistent with area postrema syndrome, likely secondary to NMOSD.

Although demyelinating CNS lesions are very rarely associated with SLE, when the 2 coexist, NMOSD is the most common demyelinating condition.³ NMOSD has also been associated with other organ and non-organ-specific autoimmunity. The most frequently found autoantibodies include antithyroglobulin and antithyroid peroxidase antibodies, antinuclear antibodies, and extractable nuclear antigens.⁸

There is a lack of Level I evidence to determine the best treatment for NMOSD. Current practice generally

Figure 2 Pathologic evaluation of the right frontoparietal lesion

(A) Hematoxylin & eosin stain shows a perivascular eosinophil (indicated with arrowhead and enlarged view in the framed panel) and numerous foamy macrophages (arrows) in the white matter. (B) Glial fibrillary acid protein highlights the astrocyte loss with a few preserved reactive astrocytes (arrows). (C) Aquaporin-4 (AQP4) immunohistochemistry indicates extensive loss of AQP4 immunoreactivity. Scale bar in A = 20 μ m. Scale bar in B = 50 μ m. Scale bar in C = 100 μ m.

dictates that acute exacerbations are treated promptly with at least 3 days of IV methylprednisolone, but sometimes longer and sometimes with a steroid taper. Many neurologists would also treat with plasma exchange, and less commonly IVIg. IVIg is slightly easier to obtain and administer in our institution than plasma exchange, thus it was chosen for our patient's treatment. Other acute and maintenance treatments to consider include rituximab (which we utilized) and cyclophosphamide (which our patient was previously treated with).^{3,9} Recently, high-dose methotrexate has also been shown to be effective for highly aggressive CNS inflammation.¹⁰

When evaluating CNS lesions in a patient with an autoimmune disease, physicians should be aware of the association with NMOSD, especially with SLE.

AUTHOR CONTRIBUTIONS

Jee-Hye Choi: study concept, writing of the manuscript. Asya Izraelit Wallach: clinical care of the patient, critical revision of the manuscript. Dominique Rosales: study concept and critical revision of the manuscript. Stefan E. Margiewicz: critical revision of the manuscript. H. Michael Belmont: clinical care of the patient, critical revision of the manuscript. Claudia F. Lucchinetti: pathologic analysis, critical revision of the manuscript. Mia T. Minen: study concept and design, clinical care of the patient, critical revision of the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES

1. Dagher AP, Smirniotopoulos J. Tumefactive demyelinating lesions. *Neuroradiology* 1996;38:560–565.
2. Sarbu N, Shih RY, Jones RV, Horkayne-Szakaly I, Oleaga L, Smirniotopoulos JG. White matter diseases with radiologic-pathologic correlation. *Radiographics* 2016;36:1426–1447.
3. Piga M, Chessa E, Peltz MT, Floris A, Mathieu A, Cauli A. Demyelinating syndrome in SLE encompasses different subtypes: do we need new classification criteria? Pooled results from systematic literature review and monocentric cohort analysis. *Autoimmun Rev* 2017;16:244–252.
4. Regev K, Nussbaum T, Cagnano E, Giladi N, Karni A. Central nervous system manifestation of IgG4-related disease. *JAMA Neurol* 2014;71:767–770.
5. Sahraian MA, Radue EW, Eshaghi A, Besliu S, Minagar A. Progressive multifocal leukoencephalopathy: a review of the neuroimaging features and differential diagnosis. *Eur J Neurol* 2012;19:1060–1069.
6. Popescu BF, Guo Y, Jentoft ME, et al. Diagnostic utility of aquaporin-4 in the analysis of active demyelinating lesions. *Neurology* 2015;84:148–158.
7. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* 2015;85:177–189.
8. Wingerchuk DM, Weinshenker BG. The emerging relationship between neuromyelitis optica and systemic rheumatologic autoimmune disease. *Mult Scler* 2012;18:5–10.
9. Vodopivec I, Matiello M, Prasad S. Treatment of neuromyelitis optica. *Curr Opin Ophthalmol* 2015;26:476–483.
10. Beh SC, Kildebeck E, Narayan R, et al. High-dose methotrexate with leucovorin rescue: for monumentally severe CNS inflammatory syndromes. *J Neurol Sci* 2017;372:187–195.

Neurology®

Clinical Reasoning: A 50-year-old woman with SLE and a tumefactive lesion

Jee-Hye Choi, Asya Izraelit Wallach, Dominique Rosales, et al.

Neurology 2017;89:e140-e145

DOI 10.1212/WNL.0000000000004386

This information is current as of September 18, 2017

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/89/12/e140.full
References	This article cites 10 articles, 0 of which you can access for free at: http://n.neurology.org/content/89/12/e140.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Demyelinating disease (CNS) http://n.neurology.org/cgi/collection/all_demyelinating_disease_cns Devic's syndrome http://n.neurology.org/cgi/collection/devics_syndrome Lupus http://n.neurology.org/cgi/collection/lupus MRI http://n.neurology.org/cgi/collection/mri Multiple sclerosis http://n.neurology.org/cgi/collection/multiple_sclerosis
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2017 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.