

Clinical Pathological Conference

Blind and Confused

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A 62-year-old man developed confusion and was diagnosed as having encephalitis. The etiology was not identified. He continued to have cognitive impairment but remained clinically stable. Five months later, he woke with bilateral vision loss. On neurological examination, he had no light perception bilaterally. The remainder of the neurological examination results were normal. Magnetic resonance imaging of the brain revealed multiple brain lesions. He was treated with steroids and plasmapheresis, with mild improvement in vision. He was then transferred to a long-term care facility, where he developed increasing confusion and ultimately died. An autopsy was performed; the differential diagnosis, neuropathology, and final diagnosis are discussed here.

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A 62-year-old right-handed man presented with acute bilateral vision loss. A few days prior to presentation, he woke up with painless vision loss in the left eye and was admitted to an outside hospital. During the hospital stay, his vision loss progressed over 2 days and involved the right eye. He was only able to see shapes and shadows. Also noted were brief episodes of flexion/extension of the knees with spasms and posturing of extremities without any change in consciousness. Initial ophthalmologic examination was notable for poor visual acuity bilaterally (OD, 20/70; OS, hand waving), relative afferent pupillary defect, and minimal disc swelling in the left eye. Slitlamp examination results were normal. No bladder/bowel symptoms, focal weakness, or sensory changes were present. He was transferred to our institution for further management.

Five months prior to his presentation, he had been admitted to an outside hospital for new onset of confusion. He was diagnosed as having viral encephalitis; however, no specific etiology was found. Magnetic resonance imaging (MRI) of the brain at that time revealed left mesial temporal T2 hyperintensity signal with edema. Results of cerebrospinal fluid (CSF) studies showed mild lymphocytic predominant pleocytosis without other abnormalities. Results of an extensive infectious workup were negative including CSF polymerase chain reaction for herpes simplex virus and antibodies to enterovirus and West Nile virus. Electroencephalography (EEG) showed left temporal epileptiform discharges; treatment with levetiracetam was started. He continued to have cognitive impairment and required constant supervision after hospital discharge.

His medical history included left renal cell carcinoma, which had been resected 1 year earlier, hepatitis C, and diabetes mellitus. He denied smoking, alcohol abuse, or use of any illicit drugs. He was a retired airline mechanic with remote exposure to trichloroethane and formaldehyde. He visited Honduras a few months prior to presentation. His medications included aspirin, levetiracetam, glipizide, crestor, and insulin.

His general examination was normal. On neurological examination, he was alert, oriented to self and time but not to place, showed perseveration, and followed simple commands. Fundo-

scopic examination was limited owing to his inability to keep his eyes still; cranial nerve examination showed poor visual acuity with no light perception bilaterally and no relative afferent pupillary defect. The remainder of the neurological examination results were normal.

Laboratory and Imaging Studies

Extensive laboratory work up was done (summarized in the Table). Pertinent findings included a positive antinuclear antibody (ANA) result, elevated erythrocyte sedimentation rate, presence of anti-Ro antibody (Sjögren syndrome antigen A), elevated anticardiolipin IgA, and presence of antiphosphatidylserine IgA and IgG antibodies. Results of CSF studies revealed an elevated protein level, increased oligoclonal bands, and elevated IgG synthesis rate.

Magnetic resonance imaging of the brain revealed T2 hyperintensities involving the basal ganglia, hypothalamus, mesial temporal lobes, optic chiasm, tectum, and periaqueductal gray matter in the brainstem (Figure 1). There was no enhancement of lesions after gadolinium administration. Computed tomography of the chest, neck, abdomen, and pelvis showed no evidence of neoplasm.

Electroencephalography showed continuous theta waves with intermittent delta activity. No epileptiform discharges were noted.

Clinical Course

He was treated with high-dose intravenous steroids for 5 days, followed by plasma exchange, with mild improvement in vision. A few days later, he developed a thrombus of the right internal jugular vein, thrombocytopenia, and melena. Endoscopy revealed esophagitis and gastric erosions. Heparin-induced thrombocyto-

penia was diagnosed. He finished 5 sessions of plasma exchange. Further hospital course was complicated by development of a right-sided multiloculated pleural effusion noted incidentally on a chest computed tomography scan (obtained for evaluation of possible malignancy), secondary to methicillin-sensitive *Staphylococcus aureus*, which was managed with decortication and broad-spectrum antibiotics. Brain MRI was repeated and showed mild improvement of lesions in the optic tract, bilateral temporal lobe, and tectum. When he was medically stable, he was transferred to a long-term care facility. A few weeks after transfer, he developed worsening of confusion and became comatose. He was admitted to an outside hospital and ultimately died. A brain MRI revealed a large frontotemporal lesion, and an autopsy was performed.

Clinical Discussion (Dr Sharma)

From the clinical presentation, it seems likely that the encephalitis and acute vision loss were secondary to the same etiology despite the 5-month interval between these two clinical problems. To make a unifying diagnosis, we considered the differential diagnosis common to both encephalitis and vision loss. The presence of left relative afferent pupillary defect on initial evaluation was suggestive of retinal, optic nerve, chiasm, and/or tract pathology. Vision loss was localized to the optic nerve, chiasm, and/or tract. This was confirmed by MRI showing involvement of the chiasm and optic tract, along with other brain lesions.

Initial differential diagnoses could have included vascular, infectious, autoimmune/inflammatory, and neoplastic etiologies.

Infectious processes must be considered in light of his visit to Central America. With involvement of the temporal lobe on both prior and current imaging, herpes simplex encephalitis was a concern. He had been treated with acyclovir, with no improvement. Furthermore, a detailed laboratory evaluation for infectious etiologies, including CSF herpes simplex virus polymerase chain reaction, was unrevealing.

Other etiologies to consider included neoplasm (central nervous system [CNS] lymphoma, optic glioma, and gliomatosis cerebri) and CNS vasculitis; however, the findings on brain imaging were not consistent with these possibilities.

Given the CSF findings, the possibility of an autoimmune/inflammatory process was very high. Results of initial serological studies were notable for several autoimmune markers including ANA, anticardiolipin antibody, and anti-Ro antibody. These findings are not specific for a particular etiology but could be seen with lupus cerebritis, paraneoplastic and nonparaneoplastic autoimmune encephalitis, Sjögren syndrome, neurosarcoidosis, neuromyelitis optica (NMO), and NMO spectrum disorders (SDs).

Neurological manifestations in systemic lupus erythematosus (SLE) vary and have been reported in more than 50% of cases, but rarely as the initial presentation of SLE.^{1,2} The American College of Rheumatology (ACR) has included 19 neuropsychiatric SLE (NPSLE) syndromes including demyelinating syndromes, seizures, acute confusional state, cranial neuropathy, movement disorders, and myelopathy.³ Optic neuritis can occur and is frequently bilateral,^{2,4} and cases of CNS lupus mimicking limbic encephalitis have been reported.⁵ Laboratory findings commonly associated with CNS lupus include elevated ANA, erythrocyte sedimentation rate, anti-

Table. Laboratory Workup

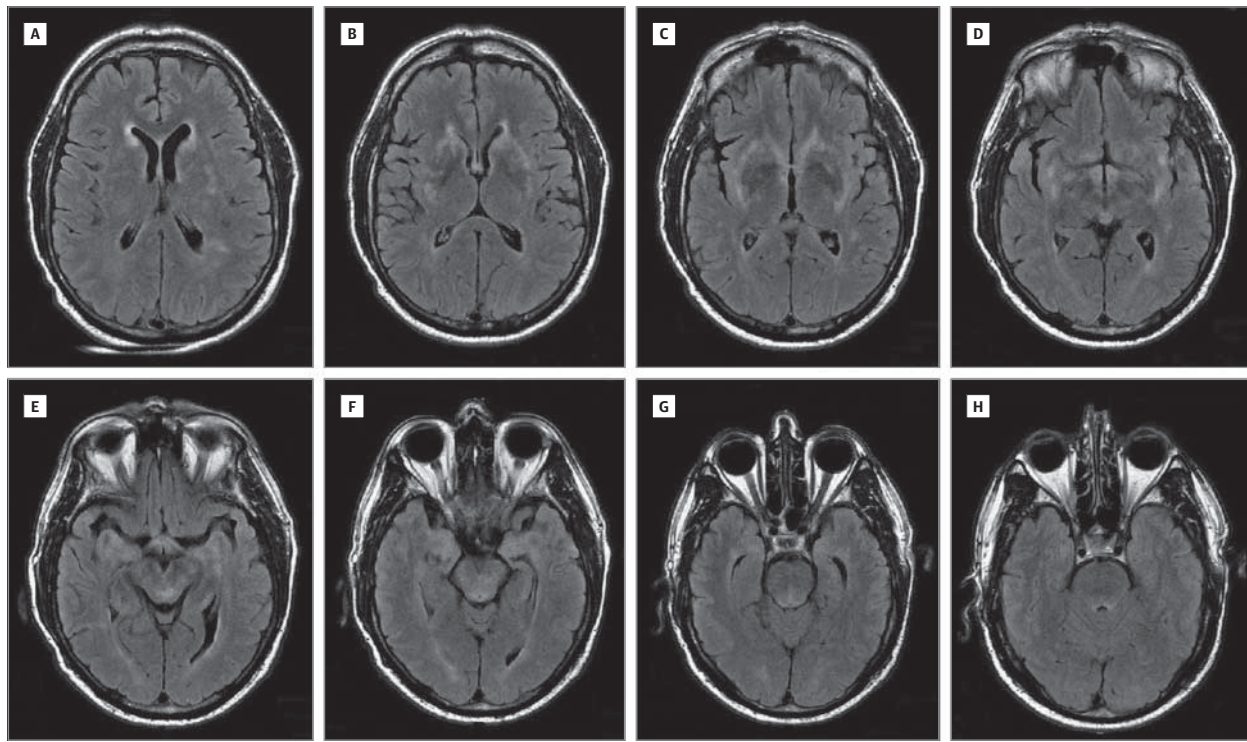
	Laboratory Tests
Routine	CBC and CMP: normal
	Thyroid-stimulating hormone: normal
	Vitamin B12: 2200 pg/mL; folic acid: 32.8 ng/mL
	ESR: 34
Autoimmune	Positive
	ANA, speckled 1:1280
	Anti-Ro Ab (SSA)
	Anticardiolipin IgA Ab (64, normal <11), normal IgG and IgM Ab
	Antiphosphatidylserine IgA Ab (50), IgG Ab (11): elevated
	B-2 glycoprotein IgA Ab >150
	Negative
	dsDNA
	Cytoplasmic ANCA, perinuclear ANCA
	Rheumatoid factor
	Anti-TPO Ab
	Anti-Smith, anti-La (SSB), anti-RNP
	Paraneoplastic panel
CSF	Glucose, 48 mg/dL; protein, 60 mg/dL; RBC count, 24/μL; WBC count, 10/μL
	ACE: normal; oligoclonal bands: positive; IgG index: 0.82; IgG synthesis rate: 16
	Cytology: negative
Infectious	Blood: negative (HIV, RPR, Lyme antibody, WNV antibodies, Quantiferon TB gold, fungal culture, Bartonella IgG, and IgM Ab)
	CSF: negative (culture, VDRL, toxoplasma Ab, cryptococcus antigen, CMV PCR, HSV PCR, WNV Ab, and enterovirus PCR)
	PPD: negative; AFB culture: negative
	Urine histoplasma antigen: negative

Abbreviations: Ab, antibody; ACE, angiotensinogen-converting enzyme; AFB, acid-fast bacilli; ANA, antinuclear antibody; ANCA, antineutrophilic cytoplasmic antibodies; CBC, complete blood count; CMP, comprehensive metabolic profile; CMV, cytomegalovirus; CSF, cerebrospinal fluid; dsDNA, double-stranded DNA; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; HSV, herpes simplex virus; PCR, polymerase chain reaction; PPD, purified protein derivative; RBC, red blood cell; RNP, ribonucleotide protein; RPR, rapid plasma reagin; SSA, Sjögren syndrome antigen A; SSB, Sjögren syndrome antigen B; TB, tuberculosis; TPO, thyroid peroxidase antibody; VDRL, Venereal Disease Research Laboratory; WBC, white blood cell; WNV, West Nile virus.

double-stranded DNA, anti-Smith antibody, antiphospholipid antibody, antiribosomal P protein antibody, and antineuronal antibodies.^{2,3} Magnetic resonance image findings can include cortical/subcortical infarcts, focal white matter lesions, and symmetric subcortical or periventricular white matter lesions, as well as optic nerve involvement.^{2,6} Cerebrospinal fluid analysis results may be normal or can show pleocytosis, elevated protein, oligoclonal bands, and elevated IgG synthesis. Diffuse slowing or focal changes may be present on EEG.² The diagnosis of CNS lupus is made if the patient has a NPSLE syndrome as defined by the ACR with 3 or more ACR (non-NPSLE) criteria for SLE.³ Our patient did not fulfill ACR criteria for CNS lupus; however, in cases of SLE where neurological features are the initial manifestation, ACR criteria for NPSLE may be fulfilled later in the course of disease.

Paraneoplastic neurological syndrome was an important consideration, especially with this patient's history of renal cell carcinoma. Classic paraneoplastic neurological syndromes affecting the

Figure 1. Brain Magnetic Resonance Image, T2-Weighted Fluid-Attenuated Inversion Recovery



Hyperintensities in the bilateral hemispheres (A), basal ganglia (B-C), hypothalamus (D), mesial temporal lobes (D-F), optic chiasm/tract (E), periaqueductal gray matter, and tectum (E-H).

brain include limbic encephalitis, paraneoplastic encephalomyelitis, paraneoplastic cerebellar degeneration, optic neuropathy, cancer-associated retinopathy, and opsoclonus myoclonus. A variety of antibodies and related cancers are associated with each syndrome. Diagnosis is made by clinical presentation, presence of paraneoplastic antibodies, and/or diagnosis of cancer.⁷

Paraneoplastic optic neuropathy presents as painless and progressive; bilateral vision loss usually occurs over days to weeks and it is often associated with other neurological disorders. Associated antibodies include anti-CV2/CRMP5-type, P/Q-type, and N-type calcium channels; anti-glutamic acid decarboxylase 65 isoform; and antiretinal transducin. Small cell lung cancer is the most commonly associated cancer, but other malignancies reported include renal cell carcinoma, papillary thyroid cancer, and thymoma.⁷ Results of CSF analysis can show mild mononuclear pleocytosis, elevated protein, oligoclonal bands, and elevated IgG synthesis.^{7,8} Brain MRI can show evidence of optic neuritis,⁸ and other brain areas can also be involved.

Paraneoplastic encephalitis has varied clinical presentations depending on the area of the brain involved (eg, limbic system, diencephalon, or brainstem) and can include acute confusion, short-term memory loss, mood changes, seizures, autonomic dysfunction, somnolence, hyperthermia, and myoclonus. The neoplasms associated include small cell lung cancer, ovarian cancer, breast cancer, testicular cancer, thymoma, and Hodgkin lymphoma.^{7,9} Cerebrospinal fluid findings are not specific but may be consistent with an inflammatory process.⁷ The MRI may be normal or may show T2 and fluid-attenuated inversion recovery

signal hyperintensity involving temporal lobes, diencephalon, and/or brainstem. The EEG can demonstrate unilateral or bilateral epileptiform discharges or background slowing if the limbic system is involved.^{7,9}

Anti-CRMP5 is known to be associated with both optic neuropathy and encephalitis, as seen in this case. It is commonly associated with small cell lung cancer, renal cell carcinoma, thyroid carcinoma, and thymoma.⁷ T2-weighted images on MRI can demonstrate hyperintensity in the striatum, with or without medial temporal lobe involvement.^{7,10} These findings were present in our patient; however, his paraneoplastic antibody testing result was negative, including specific testing for anti-CRMP5 antibody. A CT scan of the chest, neck, and abdomen/pelvis did not show any evidence of neoplasm.

Another important consideration is neurosarcoidosis, which is known to cause diverse neurological manifestations and can involve any part of the nervous system. There is a predilection for cranial nerves and leptomeninges but parenchymal involvement of the brain and spinal cord has also been reported. On imaging, lesions are often asymmetric, nodular, and contrast enhancing. Tissue biopsy may be required for definitive diagnosis.¹¹ In this case, neurosarcoidosis is less likely based on neuroimaging features and no signs of systemic sarcoidosis.

Recently, NMO SDs have gained attention both by clinicians and researchers because of the recognition of more diverse presentations and evolving understanding of the pathobiology of these disorders. Neuromyelitis optica SD is associated with antibodies against aquaporin 4 (NMO IgG) but does not meet the

Wingerchuk clinical diagnostic criteria for definite NMO.¹² Clinical manifestations include unilateral/bilateral vision loss, sensory loss in extremities, bladder dysfunction, paroxysmal tonic spasms of the trunk and limbs, intractable nausea, hiccups, and hypersomnolence.^{12,13} Optic neuritis may be unilateral or bilateral and can have involvement of the chiasm.^{12,13} Brain symptoms as initial manifestations can be seen in some cases.¹⁴ Along with positive NMO antibody test results, patients are also reported to have positive ANA, antiphospholipid antibody, Sjögren syndrome antigen A, and other autoimmune antibodies test results.^{12,13} Results from CSF analysis can show elevated protein and pleocytosis. Oligoclonal bands are uncommon and the IgG index is usually within the normal range or only mildly elevated.¹³ On MRI of the brain, 60% of cases have lesions, commonly involving sites of high aquaporin 4 expression—the hypothalamus and the periaqueductal brainstem regions surrounding the ventricular system. Lesions involving the corpus callosum, diffuse white matter, basal ganglia, or bitemporal lobes have also been reported, and they can be associated with extensive vasogenic edema.¹²⁻¹⁵ Lesions involving the bilateral hypothalamus and tissue surrounding the third and fourth ventricle or aqueduct of Sylvius are considered characteristic of NMO.^{12,13} Based on the patient's presentation and laboratory, CSF, and imaging findings, diagnosis of NMO SD seems most likely; however, MRI of the spine did not show spinal cord involvement. Further testing to look for aquaporin 4 antibodies would have been important.

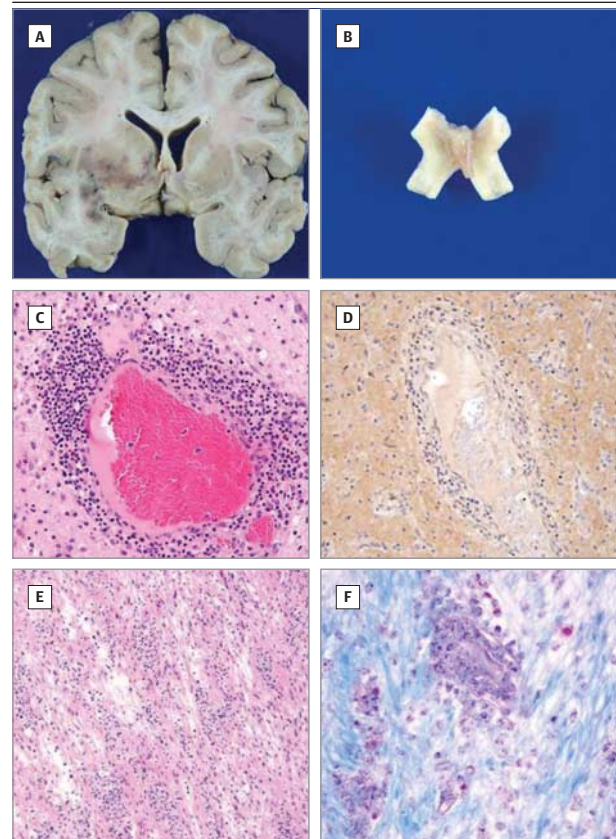
Neuropathological Discussion (Drs Malafrente and De Simone)

The serum NMO (aquaporin 4) antibody test result was positive. Gross examination of the brain was significant for an ill-defined softening and discoloration of the left paraventricular centrum semiovale, left neostriatum, internal capsule (Figure 2A), left hippocampus and subicular white matter (with associated hippocampal atrophy), left fornix, medullary tegmentum, and optic chiasm (Figure 2B). There was questionable subventricular gliosis, but most of the rest of the brain and spinal cord demonstrated neither focal lesion nor pathologic abnormality.

Microscopic sections were prepared from 20 CNS regions including the neocortex, basal ganglia, thalamus, hippocampus, brainstem (3 levels), cerebellum, corpus callosum, and spinal cord (cervical and thoracic). Sections of the left neostriatum demonstrated an ill-defined necrotizing lesion marked by acute neuronal necrosis, white matter rarefaction, and foamy macrophage infiltration. Associated with this were multifocal perivascular chronic inflammatory infiltrates consisting of lymphocytes, plasma cells, conspicuous eosinophils, and increased numbers of activated microglia (Figure 2C). Immunostaining of the lesion revealed decreased perivascular glial fibrillary acidic protein and aquaporin 4 staining, with relative preservation of myelin basic protein staining (Figure 2D).

Similar perivascular inflammatory infiltrates and increased microglia were identified, to varying degrees, in most brain sections including the grossly unremarkable basal ganglia on the opposite side. Similar necrotizing lesions were identified in the left pontine tegmentum, right splenium of the corpus callosum,

Figure 2. Images and Stainings of the Brain



A, Ill-defined hemorrhagic/necrotic lesion in the left basal ganglia and temporal lobe isthmus. B, Tan gliotic-appearing optic chiasm. C, Poorly delineated destructive lesion with macrophages and marked perivascular chronic inflammation with prominent eosinophils (hematoxylin and eosin stain; original magnification $\times 400$). D, Loss of normal aquaporin 4 immunostaining around the vessels within the lesion (aquaporin 4; original magnification $\times 200$). E, Destructive lesion of the optic chiasm (hematoxylin and eosin stain; original magnification $\times 100$), with prominent macrophages containing periodic acid-Schiff-positive digested myelin material (F, Luxol fast blue-Periodic acid-Schiff; original magnification $\times 400$).

and left middle cerebellar peduncle. Sections of the optic chiasm showed severe chronic active demyelination with relative axonal preservation, marked by decreased Luxol fast blue staining and SMI-31 immunopositivity, respectively (Figure 2E and F).

Sections of the left hippocampus revealed remote ischemic injury, demonstrated by near-total loss of CA1-CA4 neurons with associated gliosis and associated secondary degeneration of the ipsilateral fornix. The right hippocampus revealed more recent ischemic injury, characterized by the presence of acute neuronal necrosis, most prominent in the CA1 region.

Sections of the spinal cord demonstrated sparse perivascular chronic inflammation in the gracile fasciculus and anterolateral white matter. These areas demonstrated a similar staining pattern with glial fibrillary acidic protein and aquaporin 4, as previously described for the lesion in the basal ganglia. Sections of the medulla revealed marked periventricular subependymal piloid gliosis with associated Rosenthal fibers and perivascular inflammation, most concentrated in the region of the area postrema.

Similar findings were identified around the third ventricle/hypothalamus, on the outer surface of the dorsal medulla, and in the subependymal regions of the pons, midbrain, and third ventricle. The neuropathologic diagnosis was NMO SD.

Conclusions

This was a complicated case because of the overlap in clinical presentation, laboratory findings, and imaging among different autoimmune/inflammatory neurological disorders. Despite the classic definition of NMO, cases continue to be reported with both imaging and histopathologic evidence of brain lesions. This

may not be surprising because the NMO IgG is directed against aquaporin 4, a water channel concentrated in astrocytic foot processes at the blood-brain barrier, a region not limited to the optic tracts and spinal cord. Moreover, the development of lesions in NMO is not often simultaneous. The discovery of the antibody and its use in clinical workup may reveal cases with both well-established and evolving lesions, as well as those cases that have not yet developed lesions in hitherto diagnostic areas. The current case underscores the importance, both clinically and pathologically, of considering NMO not as a single disease limited to the optic tract and spinal cord, but as a spectrum of disease with clinical and pathologic manifestations that vary along spatial and temporal domains.

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