DIAGNOSTIC AND TREATMENT CHALLENGES OPEN ACCESS

Encephalitis and Myelitis in a Young Woman

Overlap Syndrome, Thyroiditis, and Occult Tumor

From the National Multiple Sclerosis Society Case Conference Proceedings

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Case Presentation

A 31-year-old woman presented with fever, ataxia, double vision, confusion, and auditory hallucinations, preceded by 2 weeks of cough, increased oral secretions, and dermatomal rash. Her medical history was unremarkable. Her family history was notable for first-degree relatives with autoimmune disorders, including Crohn disease and immune thrombocytopenic purpura.

On initial examination, she was intubated, febrile (≥38.5°C), and comatose. She had right leg hyperreflexia and exhibited autonomic instability, characterized by labile blood pressures (systolic/diastolic [86–161/21–96] mm Hg) and heart rate (50–117 bpm), requiring intermittent administration of vasopressors.

Brain MRI, head and neck CT angiogram, chest CT, and EEG were unremarkable. Serologic studies demonstrated low TSH (TSH <0.015 IU/mL), high T4 (free T4, 16.7 ng/dL), elevated antithyroid peroxidase (93 IU/mL; 0.0–8.9), thyrotropin receptor (9.67 IU/L; 0.0–1.75), and thyroglobulin antibodies (1,917 IU/mL; 0.0–1.9).

Thyroid ultrasound was consistent with thyroiditis. Initial CSF studies showed a pleocytosis (90 cells/mm^3; 97% lymphocytes), normal total protein (39 mg/dL), and normal glucose (47 mg/dL). Despite treatment for possible CNS infection with ceftriaxone, vancomycin, and acyclovir, and with dexamethasone and methimazole for possible thyroid storm, further neurologic decline prompted transfer to our hospital.

Repeat brain MRI (figure 1) showed a punctate focus of diffusion restriction with apparent diffusion coefficient correlation along the wall of the left lateral ventricle with no enhancement, whereas spinal MRI demonstrated multiple short-segment T2 hyperintensities within the cervical and thoracic spinal cord with associated enhancement (figure 1). EEG revealed background slowing without epileptiform discharges. Repeat CSF analyses revealed WBC of 139 cells/mm^3 (90% lymphocytes), mildly elevated protein (69 mg/dL), normal glucose (58 mg/dL), and 5 CSF-restricted oligoclonal bands. Extensive infectious disease workup in the CSF, blood, and sputum was negative. CSF and serum Mayo Clinic autoimmune encephalopathy panel revealed positive anti-aquaporin-4 antibody and negative antimyelin oligodendrocyte glycoprotein antibody (MOG-Ab) in serum and positive anti-N-methyl-D-aspartate receptor (NMDAR) and anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) antibodies in the CSF.

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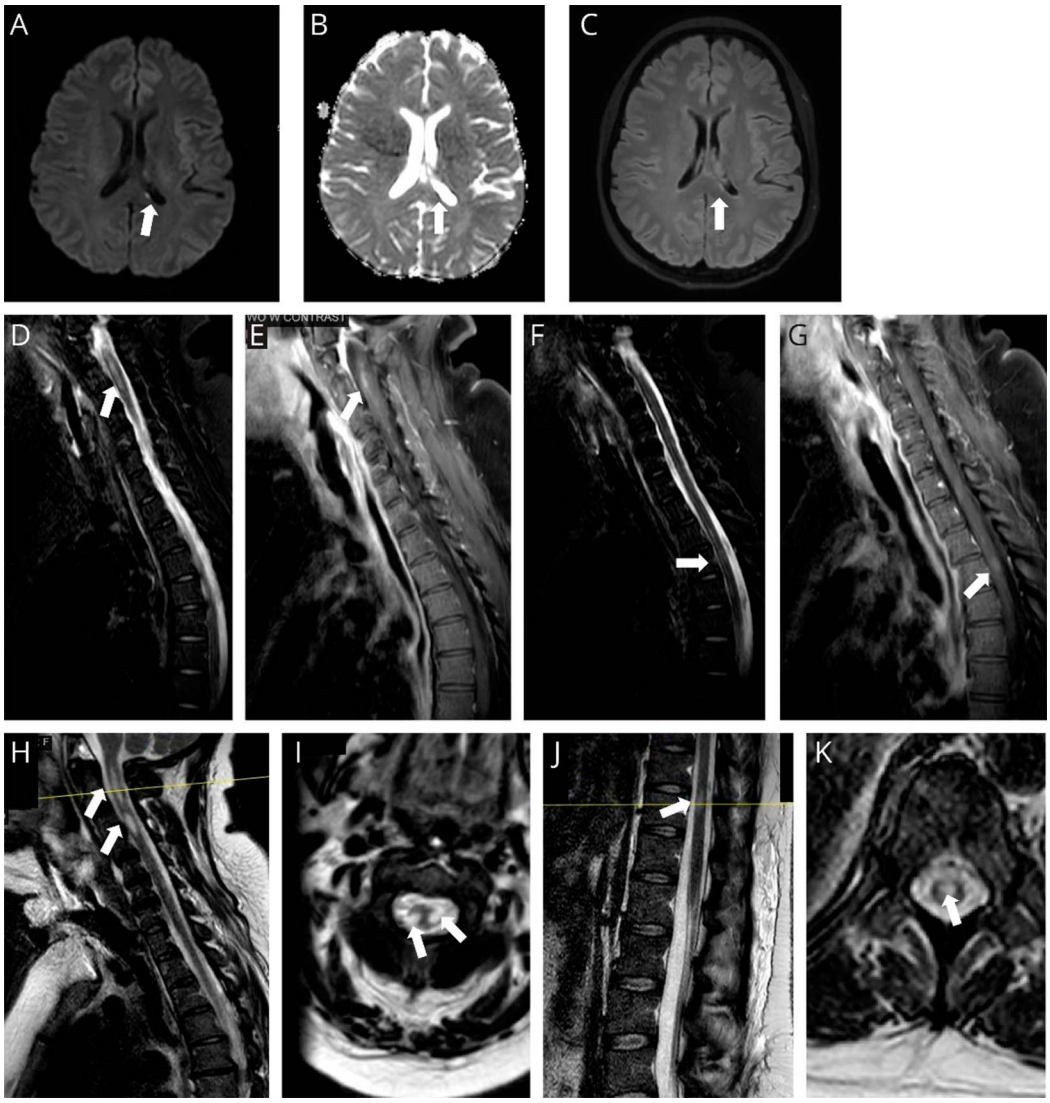
Figure 1 Brain and Spine MRI Demonstrating Multifocal Involvement



(A–C) Demonstrates a tiny focus of diffusion restriction with ADC correlation along the wall of the left lateral ventricle suggesting ischemic changes. There was no enhancement. (D–G) Demonstrates T2 hyperintensities in the upper cervical cord (D) with associated enhancement on T1 postcontrast images (E). Panels F and G demonstrate T2 hyperintensities in the thoracic cord with associated enhancement (G with arrow). (H–K) Demonstrates T2 hyperintensities in the upper cervical cord from C1 to C4, mostly involving the lateral funicular white matter (I with arrows). Panel J demonstrates T2 hyperintensities at approximately the T10 (arrow) level mostly involving the central cord (K with arrow), potentially including the interomediolateral cell columns (containing the preganglionic autonomic neurons) and the most medial aspects of the thoracic corticospinal tracts in the lateral white matter funiculi. ADC = apparent diffusion coefficient.

Differential Diagnosis

This patient presented with a subacute, progressive encephalomyelitis resulting in coma and autonomic instability. The differential diagnosis of encephalomyelitis includes infections, CNS demyelinating diseases, rheumatologic diseases, paraneoplastic/autoimmune syndromes, Hashimoto encephalopathy, as well as systemic and CNS vasculitides (table 1).

Members of the herpes family of viruses, most prominently varicella-zoster virus (VZV), are a major consideration in patients who present with symptoms implicating a process with broad dissemination throughout the CNS. VZV can produce a diversity of neurologic complications including encephalomyelitis, longitudinal serpiginous-enhancing lesions, and, less often, short-segment lesions of the spinal cord.[1]

Paraneoplastic screening performed by CT of the chest, abdomen, and pelvis revealed a large adnexal mass consistent with ovarian teratoma, prompting bilateral salpingo-oophorectomy. As previously mentioned, anti-NMDAR and anti-AMPAR antibodies were ultimately found in our patient's CSF. Repeat EEG showed rhythmical delta slowing but no obvious delta brush (defined as rhythmic delta activity of 1–3 Hz combined with synchronized paroxysmal bursts of 20–30 Hz beta activity "riding" on each wave of delta activity) that can be observed in about 30% of adults with anti-NMDAR encephalitis.[2]

Table 1 Differential Diagnostic Considerations of Encephalomyelitis

Disease classification	Diagnostic considerations
Infection	Herpes viruses, Lyme disease, and West Nile virus
CNS demyelinating diseases	NMOSD, MOGAD, ADEM, MS, and Marburg MS
Rheumatologic diseases	SLE, Sjogren, and Behçet disease
CNS malignancy	Lymphoma and glioma
Granulomatous diseases	Neurosarcoidosis
Paraneoplastic/autoimmune syndromes (cell surface/ synapse, intracellular antibodies)	Anti-NMDAR encephalitis, progressive encephalomyelitis with rigidity and myoclonus
Thyroid	Hashimoto encephalopathy
Vasculitides	Primary CNS vasculitis/granulomatous angiitis, illicit drug induced (cocaine, amphetamine, and heroin), and CNS involvement from systemic vasculitis

Abbreviations: ADEM = acute disseminated encephalomyelitis; MOGAD = myelin oligodendrocyte glycoprotein antibody disorders; NMDAR = N-methyl-D-aspartate receptor; NMOSD = neuromyelitis optica spectrum disorder; SLE = systemic lupus erythematosus; TPO = thyroid peroxidase antibody.

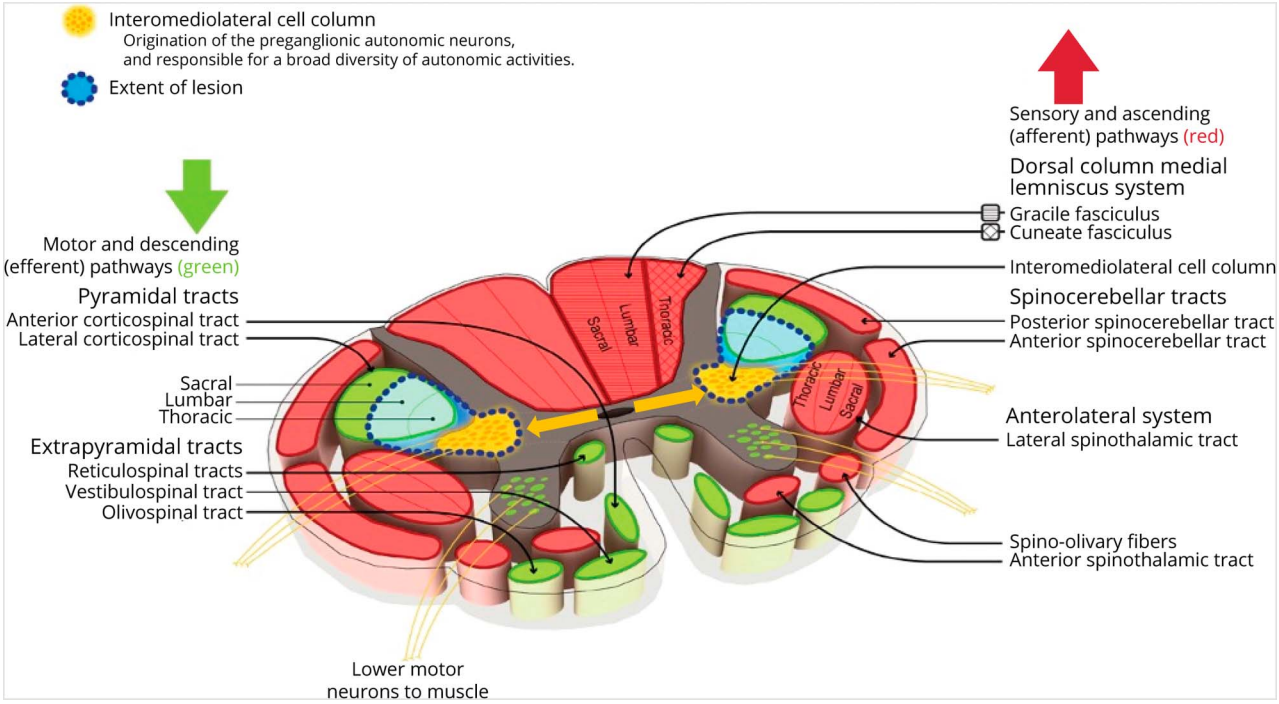
Autonomic instability, which is commonly associated with anti-NMDAR encephalitis, was a key feature of this patient's presentation. Although the precise mechanistic basis for this association remains enigmatic, focal lesions have implicated a diversity of neuroanatomic targets including insular cortex, anterior cingulate cortex, ventromedial prefrontal areas, as well as autonomic circuitries in the amygdala, hypothalamus, brainstem, and spinal cord.[3]

The presence of asymmetric pyramidal signs, in addition to the autonomic instability, prompted spinal cord imaging in our patient, which revealed cervical and thoracic spine lesions. Autonomic instability can occur in spinal cord lesions because of the interruption of sympathetic preganglionic neurons within the interomediolateral cell column in the most lateral point of the central gray matter, spanning from T1-L2, and localized just medial to the lateral corticospinal tracts (figure 2).

Final Diagnosis and Treatment

Overlap syndrome characterized by anti-NMDAR and anti-AMPAR antibody mediated encephalitis with seropositive neuromyelitis optica spectrum disorder (NMOSD) associated with autoimmune thyroiditis and ovarian teratoma.

Figure 2 Cross-sectional Schematic Drawing of the Thoracic Spinal Cord



Illustrates how the juxtaposition of the interomediolateral cell columns and lateral corticospinal tracts may explain how the lesion at T10 (see arrow in Figure 1K) caused the patient's pyramidal signs and autonomic instability. In particular, we demarcate, with a dotted blue region of interest, the close juxtaposition of the preganglionic autonomic neurons in the interomediolateral cell columns (in orange; and also demarcated by the orange arrows) and the descending lateral corticospinal tracts (which at this level of the thoracic spinal cord) would impair the upper motor neuron function of the lower extremity, potentially explaining our patient's combination of pyramidal signs in conjunction with autonomic instability.

Table 2 Immune Treatment Considerations for Overlap Syndromes

First-line therapy	Second-line therapy
IVMP 1 g daily for 3–5 d[a]	Rituximab
PLEX; 1 full volume every other day for a total of 3–7 treatments	Cyclophosphamide
IVIg 2 g/kg over 2–5 d[b]	Combination of rituximab and cyclophosphamide[c]

Abbreviations: IVMP = IV methylprednisolone; PLEX = plasma exchange.
[a] IVMP can be combined with plasma exchange.
[b] Sequencing can be a key factor in seriously ill patients in whom IVIg is not effective, and then, PLEX removes this expensive therapy. We therefore advocate for PLEX first, and IVIg subsequently, especially in very ill patients.
[c] Combination of rituximab and cyclophosphamide can be used if no meaningful recovery occurs.

After excluding infectious and neoplastic causes of encephalomyelitis, immunotherapy should be started for possible autoimmune/inflammatory conditions while waiting for confirmatory testing (table 2).[4]

Our patient demonstrated only partial benefit after 5 days of IV methylprednisolone at 1 g daily, followed by 5 sessions of plasma exchange, thereby prompting treatment intensification with rituximab and cyclophosphamide. Furthermore, her clinical course was complicated by seizures and abnormal hyperactive movements, which responded well to antiepileptic medication and benzodiazepines.

She was discharged on a 2-month prednisone taper and received monthly cyclophosphamide for 6 months followed by rituximab every 6 months. Removal of the tumor is a key consideration in exacting clinical remission, in those with confirmed evidence for a paraneoplastic process. Therefore, our patient underwent removal of the ovarian teratoma.

Discussion

The unique clinical and paraclinical phenotype of anti-NMDAR encephalitis was initially described in 2007 by Dalmau et al. with most patients presenting with prodromal symptoms, such as headache, fever, nausea, vomiting, diarrhea, or upper respiratory tract symptoms followed by profound psychiatric symptoms. If not treated early, patients with anti-NMDAR encephalitis may experience decreased responsiveness, seizures, highly conspicuous movement disorders, and/or autonomic instability.[5]

Although autonomic instability can occur in anti-NMDAR encephalitis, spinal cord lesions are generally not considered to represent the etiologic basis for such a conspicuous and potentially dangerous concomitant semiology of the anti-NMDAR syndrome. However, the presence of asymmetric extremity hyperreflexia prompted an MRI of the spine revealing multiple short-segment T2 hyperintense lesions within the cervical and thoracic cord. The discovery of serum aquaporin-4 antibody (AQP4)-Abs helped explain her inflammatory myelopathy from coexisting NMOSD. The evidence in our case is highly suggestive of an "overlap" syndrome[5-7] (table 3).

The probability of having an associated tumor in anti-NMDAR encephalitis is varied and dependent on age, sex, and ethnic background.[8,9] In the second disorder of our "overlap" syndrome patient, it should be underscored that, in rare instances, NMOSD has been associated with a paraneoplastic process. Breast carcinoma is the most common neoplasm reported with paraneoplastic-related NMOSD, but a multitude of other neoplasms have also been described.[10]

In a case of NMOSD with concomitant ovarian teratoma, histologic studies demonstrated the presence of neural tissue containing AQP4-epitope–expressing cells in conjunction with the presence of inflammatory infiltrates; again, raising the specter of the autoimmune nidus for generating autoantibodies capable of fomenting serious immune-mediated disorders, which afflict our patients.[11]

Our patient was also found to have CSF anti-AMPAR-specific antibodies, which are strongly associated with an occult neoplasm (in excess of 50% of the cases) with lung, breast, thymus, and ovarian teratoma representing the most frequently identified neoplasms. Hence, the co-occurrence of

Table 3 Paraclinical Studies for Diagnosis of Anti-NMDAR Encephalitis

Investigation	Prevalence[11]	Characteristics
MRI abnormalities	33%	T2/FLAIR hyperintense lesions
EEG findings	90%	Extreme delta brush pattern, codified by a predominance of 1–3 Hz delta activity, with superimposed paroxysmal bursts of 20–30 Hz beta activity can be seen in this syndrome. Electrographic patterns of focal or generalized slowing, punctuated by epileptiform discharges, or with ictal activity in isolation[2]
CSF findings	79%	Lymphocytic pleocytosis, normal or mildly increased protein concentration, and the presence of CSF-specific oligoclonal bands[12]
PET scan	Unknown	Marked medial occipital lobe hypometabolism by dedicated brain FDG-PET/CT may serve as an early biomarker for discriminating anti-NMDA receptor encephalitis from other AE

Abbreviations: AE = autoimmune encephalitis; FDG = fluorodeoxyglucose; FLAIR = fluid-attenuated inversion recovery; NMDAR = N-methyl-D-aspartate.

Table 4 Frequency and Significance of Concurrent Glial (Glial-Ab) or Neuronal Surface (NS-Ab) Antibodies in Patients With Anti-NMDAR Encephalitis

Concurrent Abs	Frequency	Specific antibodies	Characteristic
Concurrent glial-Ab and anti-NMDAR Ab	71%	• MOG (57%) • GFAP (33%) • AQP4 (10%)	• Older • More frequent previous episodes of encephalitis or demyelinating disorders • More frequent prodromal symptoms • Shorter duration of symptoms at diagnosis • Lower number of typical symptoms of anti-NMDAR encephalitis • More frequent CSF pleocytosis
Concurrent NS-Ab and anti-NMDAR Ab	29%	• Anti-AMPAR (50%) • GABAaR (42%) • GABAbR (8%)	• Brain MRI changes[b] • Presence of uncommon comorbid conditions[c] • Identification of atypical tumors

Abbreviations: AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; GABAaR = anti-gamma-aminobutyric acid A receptor; GABAbR = anti-gamma-aminobutyric acid B receptor; GFAP = glial fibrillary acidic protein; MOG = myelin oligodendrocyte glycoprotein; NMDAR = N-methyl-D-aspartate receptor.
[b] Abnormalities restricted to bilateral medial temporal lobes in 67% of those with anti-AMPAR Ab and involving multifocal corticosubcortical regions in 60% of those with GABAaR Ab.
[c] One breast cancer and 1 neuroblastoma.

AQP4-Ab, anti-AMPAR-Ab, and anti-NMDAR-Ab in our patient is highly suggestive of a paraneoplastic syndrome in the setting of ovarian teratoma.[12]

Concurrent Antibody-Mediated Syndromes: "Overlap"

A study by Martinez-Hernandez et al.[12] investigated the frequency and significance of concurrent glial (glial-Ab) or neuronal surface (NS-Ab) antibodies in anti-NMDAR encephalitis. Concurrent antibodies were identified in 4% of patients consecutively diagnosed with anti-NMDAR encephalitis and in 7.5% of patients with anti-NMDAR encephalitis when rescreened retrospectively (table 4). Among the 6 patients with both anti-NMDAR and anti-AMPAR antibodies, all had severe symptoms of anti-NMDAR encephalitis and decreased level of consciousness, and required admission to the intensive care unit. Four patients showed bilateral medial temporal lobe MRI abnormalities, and 5 had tumors (4 ovarian teratoma and 1 breast cancer).[12]

Identification of antibody status advances the diagnostic plan and avoids overlooking underlying conditions that can have important prognostic implications on morbidity and mortality. For instance, patients with concurrent anti-NMDAR-Ab and NS-Ab exhibited worse outcomes when compared with those with concurrent anti-NMDAR-Ab and glial-Abs, with the latter antibody designated cases achieving the categorical designation of "substantial recovery" in 89%.[12] The authors of this study recommend testing for NS-Abs and a broad search for the presence of an occult neoplasm be performed in anti-NMDAR encephalitis along with concurrent NS-Ab (e.g., anti-AMPAR-Ab).

An investigation by Titulaer et al.[13] revealed that 3.3% of 691 patients with anti-NMDAR encephalitis had *overlap demyelinating syndromes*, with concurrent or discrete demyelinating episodes, including patients with coexisting AQP4 or MOG antibodies. Patients with overlap syndromes were less likely to harbor an occult ovarian teratoma, making our case a departure from this trend. It is important that patients with overlapping demyelinating episodes tend to present with more prominent neurologic deficits and require more intensive immunosuppression to achieve and maintain a durable remission.

Conclusion

Our case, although a rare example of simultaneous acute paraneoplastic neuromyelitis optica-, anti-NMDAR-, and anti-AMPAR-positive meningoencephalitis, highlights key aspects of neuroimmunologic evaluation, including the most pertinent clinical pearl, that, although often true, Occam's razor is a logical heuristic; not a natural law. Occam's razor is the principle of parsimony, whereby the simplest explanation is usually the correct one. Alternately, and as our case report emphasizes, "A man or woman can have as many diseases as they darn well please"; the so-called Hickam's dictum.[14] Therefore, all necessary and dangerous potential diagnoses must be ruled out.

The second pearl is taking key details of the patient's hospital course and examinations into consideration when ordering different tests. Autonomic instability with pyramidal signs increased the pretest probability of identifying treatable spinal cord lesions, lesions that were in fact identified.

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