

## CLINICAL CARE CONUNDRUMS

## Chance Favors the Prepared Mind

The approach to clinical conundrums by an expert clinician is revealed through the presentation of an actual patient's case in an approach typical of a morning report. Similarly to patient care, sequential pieces of information are provided to the clinician, who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.



This icon represents the patient's case. Each paragraph that follows represents the discussant's thoughts.

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A previously healthy 18-year-old woman living in the Pacific Northwest was brought in by her parents to a local hospital with a 4-day history of "acting crazy." Two weeks prior to presentation, she complained of a new-onset severe headache, diaphoresis, and chills. Four days prior to presentation, she became progressively more impulsive, which ultimately included jumping out of a moving vehicle and running away from home. She experienced unexplained emotional outbursts and was unable to identify familiar relatives or common objects. Additionally, she began having hyperventilation spells and auditory hallucinations.

In an adolescent presenting with erratic behavior, one should consider the possibility of substance abuse or a psychiatric disease such as bipolar disorder with manic features, psychotic manifestations of severe depression, or early schizophrenia. However, it is important to first rule out non-psychiatric disease, with a diagnostic approach dependent on her human immunodeficiency virus (HIV) status. The presence of headache, diaphoresis, and chills raises concern for an infectious or noninfectious inflammatory central nervous system process. In addition to the effects of illicit drugs such as cocaine or methamphetamine, this presentation may be consistent with a medication- or herbal-induced anticholinergic syndrome, which may present with confusion, ataxia, coma, and cardiopulmonary failure. Since this case originates in the Northwest, one should be aware of the regional outbreak of *Cryptococcus gattii* in immunocompetent hosts, and that local hallucinogenic plants, such as jimson weed or mushrooms (*Amanita muscaria*) can cause anticholinergic syndromes. At this point, the differential diagnosis is broad, and evaluation should focus on potentially reversible life-threatening conditions; in particular, herpes encephalitis. In addition to a detailed history, examination, and routine laboratory studies including HIV serology, I would obtain a drug screen, and order a computed tomography (CT) scan of the brain

before performing a lumbar puncture. I would also order a magnetic resonance imaging (MRI) study to evaluate for meningel or cerebral enhancement suggestive of encephalitis.



The patient had no past medical, psychiatric, or surgical history and took no medications. She lived with her parents who thought she neither used illicit drugs or alcohol, nor was sexually active. She had recently graduated high school and was planning to attend college. Her family history was notable for a mother with bipolar and seizure disorders, and 2 healthy younger siblings. Her family had a healthy cat and dog, and reported a large number of bats living nearby. She had never traveled outside the western United States. The patient presented in late spring, but there was no obvious history of mosquito bites. Her last menstrual period was 4 months prior to presentation. Full review of systems was otherwise negative.

The family history of mood disorder supports continued consideration of bipolar disorder with psychotic manifestations. However, infectious or inflammatory processes remain highest on the differential at this point. The duration of symptoms makes common bacterial meningitis etiologies (*Streptococcus*, *Neisseria*, *Haemophilus*, *Listeria*) less likely, but would be consistent with herpes simplex encephalitis or lupus cerebritis. Additional infectious considerations would include other viral (eg, varicella zoster virus, Epstein-Barr virus, enteroviruses, and the arthropod-borne encephalitides) or unusual bacterial encephalitic syndromes. Although the health status of pets is rarely helpful, dogs can carry ticks that harbor *Borrelia burgdorferi* (the agent of Lyme disease), which may present with central nervous system (CNS) manifestations. Other conditions associated with pets (such as leptospirosis or cat scratch disease) seem unlikely. The exposure to bats raises the possibility of rabies infection. If she is HIV-positive, one would need to consider the possibility of opportunistic infections such as cytomegalovirus (CMV), *Cryptococcus*, cerebral toxoplasmosis, and progressive multifocal leukoencephalopathy (PML) caused by JC virus reaction. Finally, regardless of history, given the patient's amenorrhea, we must perform a pregnancy test.



The patient's temperature was 97.3°F, heart rate 129 beats per minute, respiratory rate 19 breaths per minute, and her blood pressure 144/97 mmHg. She was an obese, well-developed young woman, who was drowsy but arousable, with marked speech latency. Her cranium and oropharynx were normal, and her neck was supple. Aside from tachycardia, her cardiopulmonary, musculoskeletal, and skin

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exams were normal. Her abdomen was obese and soft, without masses or organomegaly. A pelvic examination was not performed. On neurologic exam, her strength was symmetrically diminished throughout (3+/5). Otherwise, she was oriented to person and general location, but not to day of week, month, or year. Her cranial nerves, sensation, deep tendon reflexes, and muscle tone were normal. A cerebellar examination, plantar response, and gait test were not performed. A brain MRI revealed only a small subarachnoid cyst and possible subtle enhancement of temporal lobes. Initial laboratory studies demonstrated: white blood cell count 14,000/mm<sup>3</sup> (72% neutrophils, 17% lymphocytes, 9% monocytes, 2% eosinophils); hemoglobin 14.0 g/dL (mean corpuscular volume 87.4 fL); platelet count 417,000/mm<sup>3</sup>. Serum electrolytes, liver function tests, coagulation studies, thyroid stimulating hormone, serum ammonia, and urinalysis were normal. Her serum pregnancy test and urine toxicology screen were negative. A room air arterial blood gas revealed a pH of 7.49, PaCO<sub>2</sub> 32 mmHg, PaO<sub>2</sub> 89 mmHg; and a bicarbonate 24 mmol/L. Cerebrospinal fluid demonstrated: red cell count of 2/mm<sup>3</sup>; white cell count 17/mm<sup>3</sup> (88% lymphocytes, 3% neutrophils, 9% monocytes); protein 19 mg/dL (normal 15–55 mg/dL); and glucose of 79 mg/dL (normal 40–80 mg/dL). Gram stain, fungal and bacterial cultures, and HIV serology were negative, and herpes simplex virus was not detected via polymerase chain reaction (PCR).

The tachycardia, respiratory alkalosis, and leukocytosis continue to suggest an infection or inflammatory state. Her neurological deterioration without focal findings, cerebrospinal fluid (CSF) lymphocytic pleocytosis with normal glucose and protein, and temporal lobe enhancement on MRI strongly suggest a meningoencephalitis. This would be an unusual presentation for most bacterial pathogens, but *Mycobacterium*, *Rickettsia*, *Listeria*, *Mycoplasma*, and *Bartonella* may rarely mimic encephalitis. Autoimmune encephalitis secondary to lupus, vasculitis, or other autoimmune disorder remains possible, but at this point an infectious encephalitis, particularly herpes encephalitis, is my highest concern. West Nile virus must be considered, but usually produces a severe illness only in immunocompromised or elderly patients. Additionally, despite the rarity of rabies, the patient's exposure to bats and the rapid clinical deterioration, suggest this possibility. In addition to routine bacterial and viral analyses (eg, enteroviral panel), samples should be sent for rabies PCR and antibody testing, West Nile virus, Lyme disease, syphilis, and mycobacterial and fungal pathogens, such as the aforementioned *Cryptococcus gattii*. Finally, given her presenting syndrome and MRI, immediate treatment with acyclovir and antibiotics is indicated.


 The patient was treated for presumed meningoencephalitis with acyclovir and ceftriaxone, but over the following several days became unresponsive to all stimuli and developed repetitive thrusting movements of her mouth, tongue, and jaw. On hospital day 10, with concern for seizures, pentobarbital coma was induced, and the patient was intubated and transferred to our facility. On arrival, her physical examination was essentially unchanged aside from being in a medical coma. Hematology, chemistries, and thyroid-stimulating hormone (TSH) were again unremarkable with the exception of an elevated creatine kinase (414 U/L) and a new anemia (hemoglobin 8.9 g/dL; mean corpuscular volume 87.6 fL) without evidence of iron deficiency or hemolysis. Blood and urine

cultures were negative. Repeat cerebrospinal fluid analysis was essentially unchanged, revealing a red cell count of 1/mm<sup>3</sup>; white cell count 20/mm<sup>3</sup> (86% lymphocytes, 2% neutrophils, 12% monocytes); protein 14 mg/dL; glucose 63 mg/dL, and negative Gram stain. Continuous electroencephalography revealed diffuse generalized slowing, but no seizure activity. An extensive evaluation for viral, bacterial, autoimmune, and paraneoplastic disorders was negative, including tests for anti-acetylcholine (ACh) receptor binding antibody, anti-striated muscle antibody, anti-N-type calcium channel antibody, anti-P/Q-type calcium channel antibodies, anto-cancer associated retinopathy (CAR) antibody (also known as anti-recoverin antibody), and anti-collapsin respons mediator protein (CRMP-5). Without confirmatory results and continued deterioration, she was empirically treated with methylprednisolone for presumed autoimmune encephalitis from hospital days 16 to 21. The patient remained unresponsive and ventilator-dependent, despite removal of all sedation. She experienced intermittent fevers as high as 40.5°C, remained tachycardic, hypertensive, and exhibited orofacial dyskinesias and jaw clenching, ultimately requiring botulinum toxin injections to prevent tongue biting. Given the lack of improvement despite attempted therapies, a working diagnosis of viral encephalitis with lasting neuropsychiatric sequelae was made. A tracheostomy and percutaneous gastrostomy tube were placed, and a long-term ventilator care facility was identified.

I continue to wonder if this may be an autoimmune encephalitis, and am concerned about her unexplained fevers. Neuroleptic malignant syndrome secondary to misuse of her parents' medications should be considered in light of the elevated creatine kinase, although the severity and duration of the syndrome seem more profound than I would anticipate. Tetanus could present with jaw dystonia, but the rest of the case does not seem to fit. At this point, considering the patient's young age and poor prognosis without identified etiology, prior to discharge I would argue for a brain biopsy looking for evidence of rabies, or other infectious or autoimmune etiologies of the patient's progressive neurologic deterioration.

 On hospital day 25, due to the persistent fevers with concern for occult abscess, an abdominopelvic CT was obtained, which identified a complex 11.8 cm × 9.0 cm adnexal mass consistent with a teratoma (Figure 1).

Given the size of the mass, it is surprising that the patient did not report abdominal symptoms and that the physicians were unable to palpate it on examination. The differential diagnosis of a complex adnexal mass in an adolescent should include an ectopic pregnancy, ovarian cysts, tubo-ovarian abscess, rarely an ovarian carcinoma or leiomyosarcoma, and a teratoma or dermoid tumor. While I mentioned the possibility of a malignancy at the outset, I did not further consider it. Common neoplasms encountered in adolescent patients include lymphoma and leukemia, germ cell tumors (including teratomas), central nervous system tumors and sarcomas, many of which have been reported to cause paraneoplastic disorders. At this point, I now think her presumed teratoma is associated with a paraneoplastic syndrome resulting in her presentation of limbic encephalitis.

 A literature search was performed by the managing clinicians who rapidly identified the association between teratoma and limbic encephalitis. The patient was initially treated with intravenous immune globulin (IVIG), with



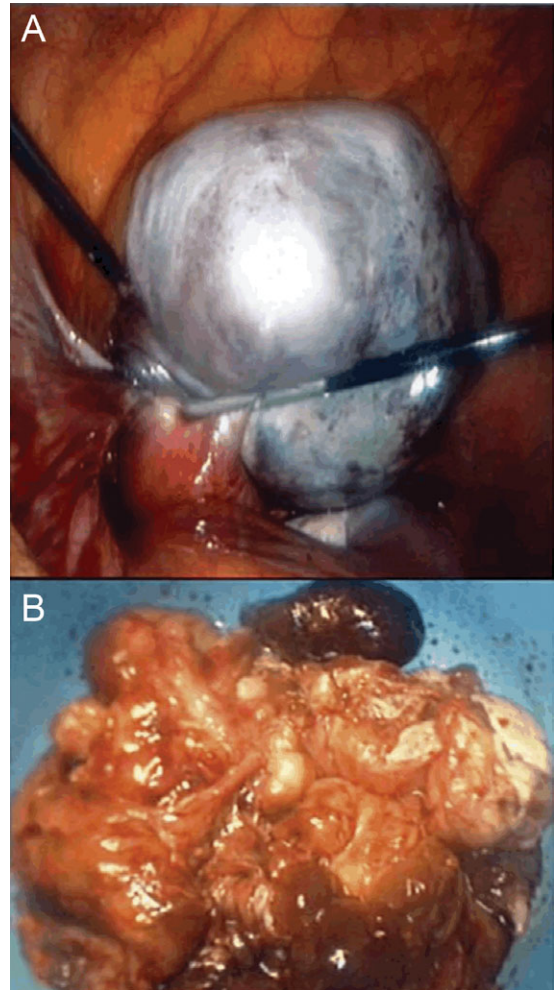
**FIG. 1.** Abdominopelvic computed tomography (CT) scan. Arrow points to a complex 11.8 cm × 9.0 cm pelvic mass originating in the left adnexa, containing fat and calcification, consistent with an ovarian teratoma.

transient improvement in her mental status. Serology returned positive for the anti-N-methyl-D-aspartate receptor antibody, confirming the diagnosis of anti-N-methyl-D-aspartate receptor encephalitis. On hospital day 36, her mass was resected (Figure 2). Pathology was consistent with a mature teratoma. Postoperatively, the patient improved daily, and was discharged on hospital day 43 with a near complete neurologic recovery. Four months following discharge, the patient had enrolled full time in college.

## COMMENTARY

The N-methyl-D-aspartate receptor (NMDAR) is an important regulator of synaptic transmission and memory within the CNS. Our patient's case illustrates the increasingly recognized syndrome of anti-NMDAR encephalitis. NMDAR hypofunction is hypothesized to result in the cognitive and behavioral abnormalities of schizophrenia, and direct antagonism of the NMDAR by drugs such as phencyclidine (PCP) and ketamine results in symptoms such as psychosis, hallucinations, delusions, agitation, and dissociative amnesia.<sup>1-4</sup> This constellation of symptoms is very similar to some of the initial neuropsychiatric symptoms observed in patients with anti-NMDAR encephalitis.

Anti-NMDAR encephalitis was first described in 2005 as a paraneoplastic limbic encephalitis associated with ovarian teratoma.<sup>5,6</sup> Characterized by the subacute onset (days to weeks) of short-term memory loss, psychiatric symptoms, and sleep disturbances, limbic encephalitis is an inflammatory process caused by autoantibodies against intracellular or extracellular antigens in the limbic system and other brain structures. Limbic encephalitides associated with antibodies to intracellular antigens (such as Hu, Ma2, CV2/CRMP5, and Amphiphysin) are more often associated with malignancies, have worse outcomes (permanent neuropsychiatric sequelae and death), and are less responsive to immune therapy. Conversely, it appears that both the paraneoplastic and non-paraneoplastic variants of limbic encephalitis associated with antibodies against cell membrane antigens (such as NMDAR and Voltage Gated Potassium Channels) respond more favorably to therapy.<sup>7</sup>



**FIG. 2.** Intraoperative and postoperative images of the patient's left ovarian teratoma. (A) Intraoperative laparoscopic resection. (B) Teratoma after resection.

As with limbic encephalitis in general, anti-NMDAR encephalitis can be non-paraneoplastic as well as paraneoplastic in etiology. In a recently published series of 44 consecutive patients with anti-NMDAR encephalitis, tumors were present in only 9 cases (8 teratomas).<sup>8</sup> When associated with a teratoma, it has been postulated that anti-NMDAR antibodies develop and cross the blood-brain barrier to target central nervous system NMDA receptors. This process results in down-regulation of the neuronal surface NMDAR which then causes the psychiatric and behavioral changes described.<sup>6</sup> The mechanism by which these antibodies traverse the blood-brain barrier is not completely understood, but likely requires some disruption of the barrier in order to trigger anti-NMDAR encephalitis.<sup>8,9</sup> Non-paraneoplastic cases evidently involve other unknown stimuli for NMDAR antibody synthesis—one report has suggested that subunits of the NMDAR are expressed by normal ovarian tissue, something which may explain the female predilection even in the cohort unaffected by teratomas.<sup>10</sup>

Most patients with anti-NMDAR encephalitis are female and young (median age 23 years), although men and children are also affected.<sup>8,9,11</sup> While the exact incidence of anti-NMDAR encephalitis is still unknown, the increasing number of case reports suggests that it may be more frequent than any other type of paraneoplastic encephalitis.<sup>12</sup> The majority of patients



with anti-NMDAR encephalitis experience an antecedent infectious prodrome (eg, diarrheal illness or upper respiratory infection [URI]), followed 10–20 days later by progressive neuropsychiatric and behavioral symptoms which include confusion, memory deficits, impaired responsiveness, seizures, central hypoventilation, and signs of autonomic instability (tachycardia, tachypnea, diaphoresis, cardiac dysrhythmia, blood pressure instability, and dysthermia). At this stage, patients may also manifest a unique constellation of choreoathetoid orofacial and limb movements such as lip licking, chewing, sustained jaw clenching, jaw opening dystonias, ocular deviation and disconjugation, grimacing, myoclonus, and bizarre arm movements. Due to cardiovascular complications and ventilator requirements, most patients require intensive care unit (ICU) level care.<sup>8,9,11</sup> As in our discussant's evaluation, other disorders to include in the differential diagnosis for this presentation includes paraneoplastic or autoimmune causes of limbic encephalitis, toxins, heavy metals, and viral causes of encephalitis; in particular, herpes simplex virus (HSV).<sup>7</sup>

The CNS imaging findings in this condition include brain MRI abnormalities in about 30%–55% of patients, which can include increased signal on fluid-attenuated inversion recovery (FLAIR) or T2 sequences of the cerebral cortex, overlying meninges, or basal ganglia. Abnormalities in the temporal lobes, corpus callosum, and brainstem have also been described. As in our patient, CSF lymphocytic pleocytosis has also been noted.<sup>6,8,9</sup>

Although many cases of limbic encephalitis portend a poor prognosis with permanent neuropsychiatric sequelae and death, anti-NMDAR can be very responsive to treatment; particularly if diagnosed early. Successful treatment of anti-NMDAR encephalitis involves immunotherapy and, preferably, early surgical resection of any tumor.<sup>6,8,9</sup> Non-paraneoplastic cases appear to require more aggressive and prolonged immunotherapies to avoid relapse. In both groups, a trend towards improved outcome has been noted in patients treated early in disease course (<40 days from symptom onset).<sup>8</sup> There are no established guidelines for the treatment of anti-NMDAR encephalitis, and no randomized controlled trials have evaluated anti-NMDAR encephalitis treatment. Observational studies of immune-modulating therapies have shown efficacy with high-dose steroids and the addition of plasma exchange and/or intravenous immune globulin. Rituximab and cyclophosphamide can be considered if patients fail to improve on other immunotherapies.<sup>9</sup> Data from case series seem to suggest a lower risk of relapse in patients treated with immunotherapy.<sup>13</sup>

Exploration of this patient's persistent high fevers ultimately led to the serendipitous diagnosis of the increasingly recognized syndrome of anti-NMDAR encephalitis, although in retrospect nearly all of the features of her presentation fit well with this condition. Thus, it was only by a chance finding on her abdominal CT scan that this patient was ultimately diag-

nosed with a treatable, noninfectious encephalitis associated with an ovarian teratoma. This case reinforces the importance of thorough patient evaluations and being prepared to draw meaningful conclusions from unexpected findings. Given how close this patient was to being discharged to a long-term care facility, we found this case a fascinating yet sobering reminder to guard against prematurely concluding a syndrome to be untreatable.

## KEY TEACHING POINTS

1. Anti-NMDAR encephalitis is an increasingly recognized cause of autoimmune limbic encephalitis, and thus should be considered in patients with new-onset psychiatric symptoms accompanied by seizures, autonomic instability, hypoventilation, or dyskinesias.
2. A thorough history, examination, and evaluation of data is critical to make an early diagnosis of anti-NMDAR encephalitis, because, unlike other forms of limbic encephalitis, this condition may be very responsive to early initiation of treatment.

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