CLINICAL PROBLEM-SOLVING

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Scratching Below the Surface

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In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.*

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On a summer afternoon, a 27-year-old Japanese woman was brought to the emergency department with a 5-day history of "strange behavior." Her illness had begun 7 days before presentation, with nausea and palpitations, followed 2 days later by short-term memory loss and anxiety. Her symptoms progressed to agitation, visual and auditory hallucinations, intermittent muscle rigidity, and involuntary jerking movements of the arms and legs.

Patients with an agitated, altered mental state often present to acute care settings such as the emergency department. Many of these patients will be described as having delirium, which is a relatively acute change in mental status that is characterized by attention deficit as its hallmark cognitive feature. Delirium may also include hallucinations and agitation, as described here. The differential diagnosis is broad and includes conditions that require urgent therapy to prevent further complications or death. An organized approach to making a diagnosis is essential and allows the clinician to select both high-yield testing and effective therapies.

In this patient, mild gastrointestinal symptoms were quickly followed by a process that appears to involve multiple areas of the brain, including the temporal lobes (which may be the source of the patient's memory loss and perhaps of her hallucinations), the parieto-occipital lobes (visual hallucinations), and basal ganglia (rigidity and involuntary movements). Given the diverse localizations of these symptoms, they are unlikely to be caused by a single focal lesion. Because of the patient's age, I would be concerned about toxic and metabolic causes, such as stimulant use, Hashimoto's encephalopathy, and demyelinating disorders (such as acute disseminated encephalomyelitis). I would also consider a broad range of diseases that cause encephalitis and meningoencephalitis, including infections (e.g., herpes simplex virus [HSV] and, given the season, West Nile virus, Saint Louis encephalitis, or western equine encephalitis), as well as autoimmune disorders such as cell-surface antibody–mediated conditions (e.g., anti–*N*-methyl-D-aspartate receptor [NMDAR] encephalitis and other paraneoplastic conditions).

The patient had previously been healthy. She lived in an apartment in Colorado with her husband and had no sick contacts. She did not smoke, drink alcohol, or use illicit drugs. Her only medication was a prenatal vitamin, although she was not pregnant. She had immigrated to the United States from Japan 5 years earlier and had not traveled recently. Her husband reported that she had been febrile at home intermittently since her symptoms began.

The presence of a fever raises concern regarding infection, but many autoimmune and paraneoplastic encephalitides and some drug-induced intoxications can also cause an elevated body temperature. The absence of reported drug use makes drug overdose and withdrawal less likely, although it does not rule them out. In any person with a possible infection of the central nervous system (CNS), but especially in those born outside the United States, a vaccination and travel history should be obtained. Although there are causes of infectious encephalitis, such as Japanese encephalitis, that are common in Asia but not in the United States, persons born in Japan are typically protected through vaccination, and the 5-year gap between immigration and presentation in the case of this patient makes a disease that is endemic to Japan unlikely. The first steps are to search for signs of CNS infection, screen for toxins, perform basic imaging of the head, and obtain cerebrospinal fluid (CSF) samples quickly.

The patient's body temperature was 37.4°C, her heart rate 123 beats per minute, her blood pressure 159/102 mm Hg, and her respiratory rate 20 breaths per minute. Her oxygen saturation was 98% while she was breathing ambient air. She was disoriented and agitated, yelling and flailing her arms and legs, and was easily provoked by noise and bright light. She was unable to follow commands and had waxing and waning attention and agitation. Her pupils were 4 mm in diameter, round, and reactive to light. A funduscopic examination revealed no evidence of papilledema. There was no facial asymmetry or tongue deviation. A neck examination revealed no nuchal rigidity. Her disorientation prohibited her from following commands for a full neurologic exam, but her strength and deep tendon reflexes were intact and symmetric, with bilateral flexor plantar responses.

The patient has profound attention and behavioral deficits with nonfocal findings on neurologic examination, which confirms diffuse cerebral involvement. The flailing movements of the arms and legs suggest a movement disorder, although it remains unclear whether these movements are voluntary. The patient's tachycardia is nonspecific and may be caused by agitation, pain, or dehydration; however, persistent sinus tachycardia has also been described in patients with certain cell-surface antibody–mediated autoimmune encephalitides (namely, anti-NMDAR encephalitis). Such patients may have autonomic hyperactivity in addition to movement disorders such as dystonia, chorea, and facial dyskinesias.

Given her agitation, sedation is indicated for CSF sampling and neuroimaging. If magnetic resonance imaging (MRI) with contrast material is not readily available, a noncontrast computed tomographic (CT) scan followed by lumbar puncture would be appropriate. In addition to basic CSF studies and bacterial culture, polymerase-chain-reaction (PCR) testing of the CSF for HSV should be performed. Empirical treatment with acyclovir should be started to treat possible HSV encephalitis, given the severe complications, including death, that can result if this condition is left untreated. Autoantibody titers should be measured in the serum and CSF to assess for anti-NMDAR and anti–alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor (anti-AMPAR) encephalitis. Ovarian teratomas have been associated with anti-NMDAR encephalitis, and removal of the teratoma has resulted in full remission; thus, I would also consider ovarian imaging, which often can be accomplished with the use of transvaginal ultrasonography in adult women.

Empirical antimicrobial therapy for bacterial and viral meningitis (intravenous vancomycin, ceftriaxone, and acyclovir) was administered in addition to intravenous fluids. A serum chemical profile, liver function tests, thyroid function tests, and complete blood count were normal. Results of urine toxicologic screening were negative for opiates, methamphetamines, cocaine, and alcohol; results of subsequent serum toxicologic screening were also negative. A CT scan of the head without contrast material showed no intracranial abnormalities. CSF obtained by lumbar puncture contained 30 leukocytes per microliter (95% lymphocytes); the glucose level was 87 mg per deciliter (4.8 mmol per liter; normal range, 40 to 80 mg per deciliter [2.2 to 4.4 mmol per liter]), and the protein level 37 mg per deciliter (normal range, 15 to 45). Gram's staining of the CSF revealed no organisms.

Over the next 12 hours, the patient became febrile, her speech became unintelligible, and her agitation worsened. Treatment with benzodiaze-

pines and haloperidol was also initiated, but the patient became combative. To facilitate further diagnostic testing under deeper sedation, endotracheal intubation was performed and mechanical ventilation initiated.

The CSF pleocytosis is consistent with an inflammatory process and makes toxic and metabolic disorders unlikely. The lymphocyte predominance and normal glucose level argue against typical bacterial causes. The focus should remain on infectious (especially viral) and autoimmune or paraneoplastic encephalitides, many of which can be characterized by this CSF profile. An MRI of the brain with contrast material remains an important next step, especially in the face of the marked clinical deterioration of the patient's condition, which suggests progression of her underlying illness despite the administration of empirical antimicrobial therapy. Most cases of HSV type 1 meningoencephalitis have characteristic T_2-weighted hyperintensities and restricted diffusion involving the temporal lobes by this stage of the illness. Autoimmune or paraneoplastic encephalitides can have a wide spectrum of findings on neuroimaging, ranging from completely normal findings (even in patients with severe clinical manifestations) to T_2-weighted or fluid-attenuated inversion recovery (FLAIR) signal hyperintensities in the hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem, and, infrequently, the spinal cord. I would order testing for HIV antibody as well as testing of serum and CSF for syphilis. I would ask the laboratory to hold a tube of CSF to allow for further testing as needed.

MRI of the brain with and without contrast material revealed no intracranial abnormalities. Transvaginal ultrasonography was performed and revealed a hyperechoic lesion (10 mm by 8 mm by 8 mm) in the left ovary. High-dose intravenous methylprednisolone treatment (1000 mg daily) was initiated. A laparoscopic resection of the left ovary was performed. Pathological analysis revealed a mature teratoma (1 cm by 1 cm) (Fig. 1).

The normal brain MRI findings and a pathologically proven teratoma in a patient in this age group presenting in this manner are virtually diagnostic of anti-NMDAR encephalitis, a cell-surface antibody–mediated paraneoplastic syndrome.

The most important treatment in these patients is removal of the teratoma. Combinations of glucocorticoids, intravenous immune globulin, and plasma exchange are typically used in conjunction with surgical removal to help clear the circulating antibodies. Immunotherapy with cyclophosphamide or rituximab is also used in some cases. Patients often make a full recovery, although this may take months.

The results of CSF testing for anti-NMDAR antibodies were positive at a titer of 1:40 (normal, <1:1), which confirmed the diagnosis of anti-NMDAR antibody–mediated encephalitis. Testing for anti-NMDAR antibodies in serum obtained at the same time was negative (titer, <1:10). Plasmapheresis was performed for 5 days, after which intravenous immune globulin was administered. Despite these therapies, the patient remained minimally responsive to verbal stimuli. She had severe autonomic instability that required intermittent infusions of vasoactive medications to treat both hypotension and hypertension. She also had orofacial dyskinesias and jerking movements. Continuous electroencephalography (EEG) confirmed recurrent electrical seizures that proved refractory to multiple antiepileptic drugs; ultimately, a pentobarbital-induced coma was required to suppress seizure activity. A burst-suppression EEG pattern was attained; after 48 hours, administration of pentobarbital was discontinued, and her mental status improved rapidly. Sedation and mechanical ventilation were then discontinued successfully.

At the time that the patient was discharged to an acute rehabilitation facility, she was taking four antiepileptic medications, which were gradually tapered. She returned home after a 6-week hospitalization and has recovered fully. She is no longer taking antiepileptic medications, and in the subsequent 2 years she has had no relapses of her encephalitis.

COMMENTARY

"Altered mental status," a nonspecific term that is frequently used to describe alterations in alertness, cognition, or behavior, is commonly encountered in the emergency setting.[1] Causes range from primary neurologic conditions, trau-

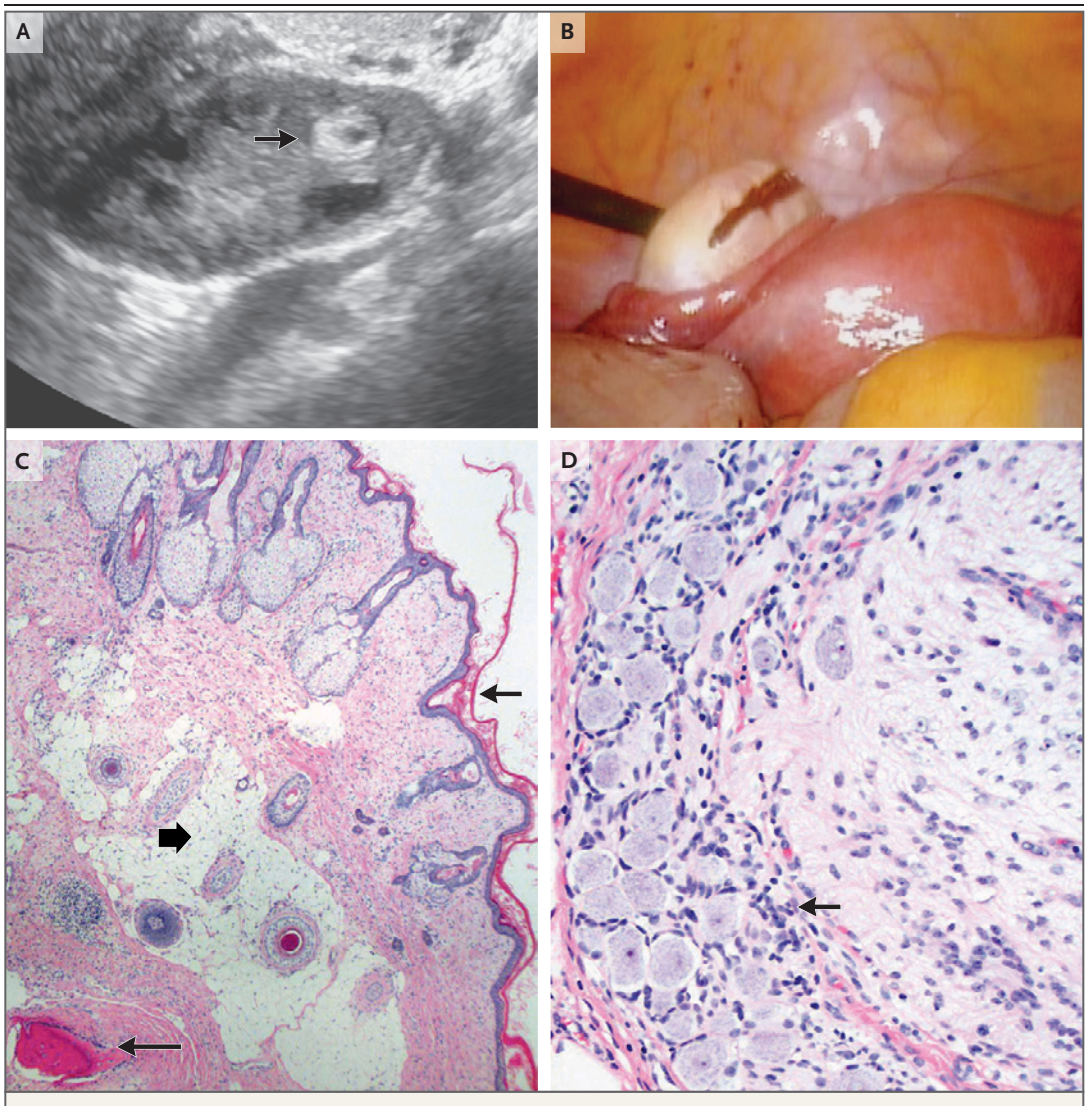

Figure 1. Mature Ovarian Teratoma.

Panel A shows transvaginal grayscale ultrasonographic imaging of the left ovary, which revealed a hyperechoic lesion, measuring 10 mm by 8 mm by 8 mm, with a central cystic focus. The presence of adipose tissue (arrow) is consistent with a dermoid cyst (teratoma). The right ovary was sonographically normal. Panel B shows the left ovary in an image obtained during laparoscopy; the teratoma itself cannot be seen because it was contained within the ovary. Panel C shows a specimen from the resected teratoma; hematoxylin and eosin staining revealed areas with skin (top arrow), adipose tissue (middle arrow), and bone (bottom arrow). Panel D is a higher-magnification view of the teratoma, showing mature ganglion cells surrounded by inflammatory infiltrates (arrow).

ma, and psychiatric disease to systemic disorders such as sepsis and metabolic or endocrine abnormalities.[1] In this case, the rapid onset of illness, unremarkable medical history, and features that suggested diffuse brain involvement led to immediate concern regarding a primary neurologic process. Drug-related and alcohol-related syndromes, metabolic disturbances, and infection were also considered. Her sex and age, as well as the presence of a hyperkinetic movement disorder, also suggested the possibility of an antibody-mediated encephalitis — particularly anti-NMDAR encephalitis, with or without an underlying tumor — because this disease predominantly affects children and young adults and is frequently characterized by dyskinesias.[2] Empirical treatment for bacterial and viral infections of the CNS was an immediate priority,

given the high morbidity and mortality associated with delayed treatment of such infections.

The term "encephalitis" describes inflammation of the brain associated with impaired cerebral function. This condition can lead to a variety of clinical manifestations, such as altered behavior, focal or generalized neurologic deficits, seizure, and fever. The most common causes of encephalitis are infectious, though in some cases the cause is never discovered.[3] Autoimmune processes account for at least 20% of all cases of encephalitis; the increasing recognition of antibodies associated with these cases continues to expand the spectrum of this illness.[3] Surface antibody–related syndromes leading to encephalitis can be caused by autoantibodies to a variety of surface antigens, including NMDAR, AMPAR, contactin-associated protein–like 2 (CASPR2), leucine-rich glioma inactivated 1 (LGl1), glycine receptor, and gamma-aminobutyric acid receptor (GABA-R).[4] Antibodies to intracellular antigens (such as Hu, CV2, Ri, amphiphysin, CRMP5, Yo, and Ma2) can also cause encephalitis and are also frequently paraneoplastic.[5] Patients with autoimmune encephalitis often present with a subacute onset of behavioral and psychiatric symptoms — such as grandiose delusions and hyperreligiosity, which can prompt psychiatric hospitalization — that subsequently progress to include dyskinesias, myoclonus or ataxia, autonomic instability, and seizures.[2]

Over the past decade, anti-NMDAR antibodies have increasingly been recognized as a cause of human encephalitis.[2] Anti-NMDAR encephalitis also occurs in some animals and was recently diagnosed in a polar bear in captivity.[6] Women make up approximately 80% of patients with anti-NMDAR encephalitis. Although the disease may affect persons of any age, it is most commonly reported among patients 2 to 40 years of age.[2]

The NMDAR is a ligand-gated ion channel that functions as a glutamate receptor on the surface of CNS neurons that play critical roles in a wide spectrum of neurologic activity, including memory and learning. In vivo and in vitro studies have suggested that autoantibodies against NMDARs cause a reversible loss of their surface density and synaptic localization, which decreases glutaminergic function. Accordingly, NMDAR hypofunction is postulated to be the mechanism underlying the psychosis and cognitive and behavioral deficits that are prominent in many patients with anti-NMDAR autoantibodies.[7]

The diagnosis of anti-NMDAR encephalitis is based on clinical presentation and is confirmed by the detection of antibodies in the CSF. Serum antibodies are frequently present, but negative tests are reported in nearly 15% of patients[8] and should not deter treatment in cases in which clinical suspicion for the disease is high.[2,9] Patients in whom the diagnosis is delayed or who have received treatment before testing are more likely to have negative results of serum antibody testing.[2] Additional CSF studies are abnormal in most cases of anti-NMDAR encephalitis and may include a lymphocytic pleocytosis (usually less profound than in viral encephalitides), mildly increased protein levels, oligoclonal bands, or an elevated IgG index (suggesting enhanced immunoglobulin production in the CSF).[2] CSF testing is critical to rule out infectious causes of encephalitis. Imaging is insensitive for detection of the disease; MRI of the brain is normal in approximately half the cases and in many other cases reveals only nonspecific changes, such as cortical or subcortical T_2-weighted or FLAIR hyperintensity.[2] EEG findings are often abnormal and include slow, disorganized activity that can be accompanied by seizures[2]; an "extreme delta brush" pattern (rhythmic delta activity at 1 to 3 Hz with superimposed bursts of rhythmic 20-to-30 Hz beta frequency activity) has been associated with the disorder but is not specific for anti-NMDAR encephalitis.[10] Recent advances in low-cost, high-throughput genetic sequencing platforms are being investigated to improve diagnostic accuracy for both infectious and autoimmune encephalitides.[11]

Triggers for anti-NMDAR encephalitis include neoplasms and preceding infection (in particular, HSV).[12] Ovarian teratomas are the type of neoplasm most commonly identified in patients with anti-NMDAR encephalitis, but other tumors have been reported (including testicular, lung, and breast tumors).[2] Anti-NMDAR encephalitis has also been described in pregnant women, both those with tumors and those without tumors. Anti-NMDAR antibodies can cross the placenta and may lead to developmental delay in the fetus.[13] Other reports have suggested a link between HSV encephalitis and the development of anti-NMDAR antibodies; the development of

these antibodies can lead to a relapse of encephalitis after recovery from the initial HSV infection.[12]

Data to guide the management of anti-NMDAR encephalitis are derived from case series and retrospective studies. Initial treatment involves removing the antibodies by means of plasma exchange or with intravenous immune globulin and then halting antibody production with immunosuppressive agents (typically glucocorticoids, with rituximab or cyclophosphamide reserved for refractory cases). Also critical is imaging to search for an ovarian teratoma, which should be removed promptly if identified.[14] Transvaginal ultrasonography can be diagnostic; however, if the study is unrevealing or not feasible, pelvic CT or MRI should be performed.[15] Treatment of autonomic instability, seizures, and severe agitation can be difficult and may require airway management and deep sedation, as was the case for this patient.[9] Antipsychotic agents such as haloperidol are frequently ineffective.[2]

Early diagnosis and treatment are associated with improved outcomes, which makes prompt recognition of the disease paramount.[14] Although death or disability can occur, approximately 75% of patients with anti-NMDAR antibodies recover either completely or substantially.[2] This may be explained by the fact that the offending antibodies are directed against a cell-surface receptor, whereas the neurons themselves usually remain intact.

This case illustrates the importance of a systematic approach to the common emergency department presentation of a patient with "altered mental status." Recognition of the association between ovarian teratomas and anti-NMDAR encephalitis enabled prompt diagnosis and treatment, with eventual full recovery.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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