Paraneoplastic Anti–*N*-Methyl-D-Aspartate-Receptor Encephalitis From Mature Cystic Teratoma

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A 20-year-old nullipara with no significant medical history presented to a local emergency department with complaint of severe headache. She was diagnosed with migraine headaches, treated, and discharged. Three days later, she re-presented with persistent and worsening headaches, memory deficit, and altered mental status. In the emergency department, she became agitated and confused and was admitted for overnight observation. She then developed generalized tonic clonic seizures and ultimately required intensive care unit (ICU) admission, intubation, sedation, and daily anti-epileptic therapy. Neurologic workup was performed including routine laboratory tests, lumbar puncture, magnetic resonance imaging of the head, and continuous electroencephalogram. Study results were negative for infectious encephalitis, intracranial mass, and epilepsy. Computed tomography of the abdomen and pelvis revealed a 1-cm left adnexal hypodensity consistent with possible dermoid cyst.

The patient was transferred to a tertiary care medical center, where her condition continued to deteriorate. She experienced continued seizure activity, without intentional movements, and no response to external stimuli. She was started on lamotrigine, levetiracetam, and topiramate, all without change in her condition. She continued to require ventilatory support and developed complications, including ventilator-associated pneumonia and right femoral deep vein thrombosis.

Given the unique presentation of such severe disease, further investigations into uncommon etiologies, such as paraneoplastic encephalitis, were performed. Extensive serum and cerebrospinal fluid (CSF) studies were assessed, including a recently developed assay for anti–*N*-methyl-D-aspartate-receptor (anti-NMDA-R) antibodies. Anti–NMDA-R antibodies were found in her serum and CSF. The patient was started on plasmaphoresis and intravenous immunoglobulin therapy. A gynecology consult was then initiated (approximately 5 weeks after initial presentation) to evaluate her suspected dermoid cyst as a possible source for these antibodies and her condition.

A transvaginal ultrasound examination revealed a 1.77×1.56-cm solid left ovarian mass suggesting a dermoid cyst (Fig. 1). The patient was taken to the operating room for diagnostic laparoscopy. Bilateral multicystic ovaries were noted and explored laparoscopically (Fig. 2). A small cyst with visible hair and serous fluid was identified and removed from the left ovary. Paraffin section of the specimen confirmed the presence of a benign cystic teratoma with neural tissue present. The specimen was not tested for NMDA-R expressing tissue. Postoperatively, the patient remained in the neurological ICU under ventilator support, with modest improvements in mental status and function. Upon discharge to a rehabilitation center, she remained unresponsive and continued to require assisted ventilation and tube feedings. During the past 5 months, she has improved significantly. She is now responsive to auditory and tactile stimuli, breathing spontaneously, and participating in

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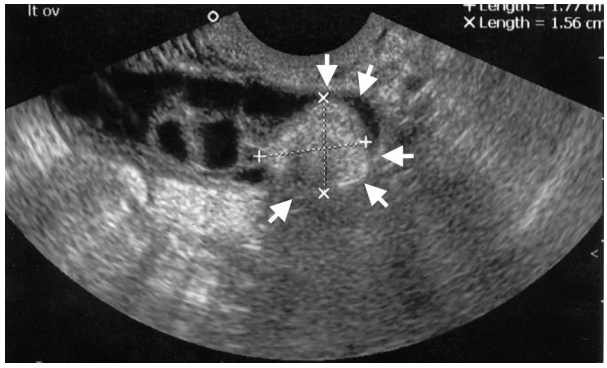

Fig. 1. Transvaginal view of the left ovary showing a 1.77×1.56-cm mass with solid and cystic components suggesting a dermoid cyst.

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daily physical, occupational, and speech therapy. The patient remains in a long-term rehabilitation facility awaiting further improvement before she can live independently.

QUESTIONS FOR THE SPECIALIST

What is anti–NMDA-R–mediated encephalitis? Can we determine the prevalence of this condition?

N-methyl-D-aspartate receptors are glycine and glutamate ligand-gated cation receptors in hippocampal neurons responsible for excitatory synaptic transmission and remodeling.[1,2] Persistent excitation of these receptors and subsequent downstream over activity is believed to be a major cause of epilepsy, dementia, and stroke. Excess production of antibodies targeting the NMDA-R may cause severe encephalitis.[1] It is postulated these antibodies are produced by the immune system after exposure to ectopic neural tissue, such as within small cell lung cancer and ovarian teratoma.[1,3,4]

Only four cases of this condition were described before 2005.[5] However, case reports now appear regularly in the medical literature and in the lay press.[6] Given the recent acceleration in reported cases, the incidence of this condition is possibly higher than previously estimated. As cases are documented and diagnostic tests (notably antibody assays and tissue analysis) become more prevalent, estimates of the true incidence will ensue.

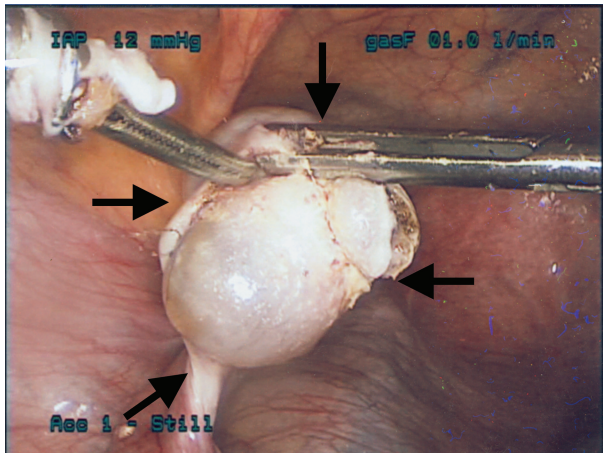

Fig. 2. Laparoscopic view of left ovary showing an ovarian cyst.

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How do patients present?

Patients present with a variety of prodromal symptoms, ranging from headache and hyperthermia to a viral-like respiratory illness. This vague presentation of nonspecific complaints may be dismissed or attributed to a variety of benign etiologies. Neuropsychiatric symptoms then develop, including anxiety, agitation, bizarre behavior, auditory hallucinations, delusions, and acute personality change.[1,4] Patients experience rapid neurological deterioration leading to seizures, dyskinesias, movement disorders, autonomic instability, and central hypoventilation. Intensive care unit admission and ventilator support is often initiated before the diagnosis is made.

What is the differential diagnosis to be considered in this patient?

Given the subtle onset and multifocal presentation, there is a wide differential. This includes toxic and metabolic disorders, autoimmune encephalitides, neuroleptic malignant syndrome, seratonin syndrome, and lethal catatonia.[7] Nearly all of these conditions have no gynecologic source, and gynecologic consultation is only requested after extensive neurologic evaluation and effective elimination of these disorders.

How is the diagnosis made?

The initial evaluation, including complete history and physical examination, basic laboratory analysis, lumbar puncture, brain magnetic resonance imaging, and continuous electroencephalogram, refines the differential diagnosis. Ultimately, patients who present with suspected NDMA-R–mediated encephalitis must undergo serum and CSF evaluation for anti–NMDA-R antibodies. Positive antibody assays in the setting of the described clinical presentation appear diagnostic of this condition.[1] If the antibodies are identified,

imaging studies including positron-emission tomography, computed tomography, and ultrasonography should be used to identify all possible sources contributing to antibody production.

What is the role of dermoid cysts in this phenomenon?

Dermoid cysts, or mature cystic teratomas, are ovarian tumors that may contain tissue derived from all three germ cell layers. The majority of dermoid cysts are asymptomatic and benign. Typically, surgical excision is recommended when patients are symptomatic, ultrasound imaging is concerning for malignancy (large size, solid component, and blood flow), or tumor markers (CA 125, β-hCG, alpha fetoprotein, testosterone) are elevated.[8] Dermoid cysts left in situ have a 0.2–2% risk of malignant transformation, with an increased risk of malignant degeneration when greater than 6 cm in size.[9] The majority of cysts can be removed laparoscopically with minimal complication (spillage and peritonitis 0.2%, adhesion formations or granulomatous reaction, recurrence 4%).[9,10]

Current clinical evidence implicates dermoid cysts in anti–NMDA-R encephalitis.[1] This is based on the large prevalence of dermoids found in these patients, the decrease in serum antibodies found after tumor removal, and the positive clinical response to tumor removal (see below). Dermoids appear to have a role in this condition by expression of neural tissue which triggers an immune response resulting in over production of anti–NMDA-R antibodies. All dermoids examined in these patients contained neural tissue, and 100% (25/25) of specimens tested were positive for NMDA receptors.[11]

What is the treatment for patients with this condition? Is resection of ovarian tumor warranted?

Given the recent identification of this condition and the variability of described cases, from spontaneous resolution to death, there is no identified treatment algorithm to date. The combination of tumor removal and immunotherapy (intravenous immunoglobulin, plasma exchange, corticosteroids) shows superior results in limited case series. In the largest single series to date, the majority of patients with suspected anti–NMDA-R encephalitis (59%, 58 of 98) had an identifiable tumor, most commonly an ovarian teratoma. Patients treated with early tumor removal (n=36) had a 72% rate of full recovery. In contrast, patients treated with late removal or no removal (n=22) had a 36% rate of full recovery. Furthermore, death occurred in one of 36 patients who had early tumor removal compared with three of 22 patients who had late or no tumor removal.[11] Thus, the limited data available supports active treatment including surgical removal of tumor when discovered.

What is the prognosis and anticipated recovery of these patients?

Outcomes of this condition vary based on time to diagnosis, neurologic deterioration at diagnosis, identification, and prompt removal of the tumor. Reports document improvement ranging from immediately after initiation of treatment (intravenous immunoglobulin, plasma exchange, corticosteroids, and/or surgery) to 16 weeks after a completed course of therapy.[1,5,6,11,12] In the largest single series to date, 17-month follow-up revealed that 47% of patients had full recovery, 28% mild stable deficits, 18% severe deficits, and 7% death.[11] In the patients who died, the diagnosis of anti–NMDA-R encephalitis was made postmortem. Therefore, while patients can, and do, recover with proper treatment, it remains a dangerous condition with significant morbidity and potential mortality. Counseling of patients and families for this guarded prognosis is essential.

Should all patients with dermoid cysts undergo serum screening for anti–NMDA antibodies?

Dermoid cysts are the most common type of benign ovarian neoplasm in reproductive-aged women, accounting for 25% of ovarian neoplasms in premenopausal women.[10] While the risk of paraneoplastic encephalitis resulting from dermoids is unknown, it remains an exceedingly rare condition, making serum screening for these patients neither practical nor cost-effective. As this condition becomes better defined, there remains a possible future role for such screening.

Is there a role for surgery in patients with suspected anti–NMDA-R encephalitis without known dermoids?

Because extremely small teratomas have been linked to anti–NMDA-R encephalitis, an intensive radiological search is warranted for teratoma at any site. However, since very small dermoids may escape ultrasound detection, an argument may be made to perform surgery, including large wedge resection of the ovary. While such an approach may result in clinical improvement, this issue remains controversial.

CONCLUSION

Anti–NMDA-R–mediated encephalitis is a newly characterized disease with potential morbidity and mortality that is devastating to patients and their families. As it is related to a common ovarian neoplasm and given its recent press in the lay literature, patients may approach their physicians regarding screening and removal of these otherwise benign ovarian lesions. Increased clinical suspicion, identification of risk factors or precipitating events for the development of antibodies, and superior treatment are all needed. Within gynecology, increased physician awareness of its possible association with dermoid cysts is critical.

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