

A Tiny Ovarian Teratoma Leading to a Life-Threatening Condition

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ABSTRACT

Introduction: Anti-N-methyl-D-aspartate receptor (NMDA-R) encephalitis is a severe condition that can be life threatening. It is occasionally associated with ovarian mature teratomas. Prompt treatment of the syndrome and the associated tumor can result in complete recovery.

Case Description: We present a case of anti-N-methyl-D-aspartate receptor (NMDA-R) encephalitis associated with a very small (9-mm) ovarian teratoma. Removal of the teratoma along with immunosuppressive therapy led to full recovery of the patient.

Discussion: This underrecognized paraneoplastic syndrome can be complex and life threatening. Quick removal of the associated tumor allows for a better prognosis. This paper includes a review of the literature.

Key Words: Dermoid, Encephalitis, Limbic, NMDA, Teratoma.

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INTRODUCTION

Anti-N-methyl-D-aspartate receptor (NMDA-R) encephalitis is a recently discovered but increasingly identified paraneoplastic syndrome.¹ It is occasionally associated with ovarian mature teratomas, also known as dermoid cysts. Typically, patients initially present with psychiatric symptoms of psychosis or confusion, at times in combination with seizure activity. The patient's condition can rapidly deteriorate into a life-threatening one. This syndrome remains underrecognized, despite a growing body of evidence, with >500 cases reported in the literature thus far. Reported cases have shown that with prompt identification and removal of the associated tumor, outcomes can be significantly improved.

We present the case of a patient who had complete recovery after excision of the involved ovary and discuss diagnosis and management, incorporating a literature re-

view. Our purpose is to familiarize clinicians with this underrecognized syndrome and the potential lifesaving benefit of timely surgical management.

CASE REPORT

A 25-year-old woman was brought to her local emergency department after being found wandering the streets behaving in a bizarre fashion, on a background of 2 weeks of worsening vision and paraesthesia in her right upper limb. Further medical history included fibromyalgia and depression, for which she was not receiving any medication.

After extensive screening for organic causes of her delirium, she was admitted to the psychiatric inpatient ward with a differential diagnosis of acute stress reaction to significant social pressures. Her condition deteriorated over the next few days, as she did not respond to her

psychotropic medication, and she was administered electroconvulsive treatment. Over the next 24 hours, she became unresponsive, with a Glasgow Coma Scale of 4, necessitating sedation, intubation, and transfer to the intensive care unit (ICU).

While in intensive care, the patient was treated empirically for meningoencephalitis pending the results of tests. Cerebrospinal fluid analysis identified an elevated lymphocyte count; however, cultures and polymerase chain reactions results were negative. Brain magnetic resonance imaging (MRI) showed no intracranial pathology. An electroencephalogram identified diffuse slowing, without epileptiform changes, however cyclical leg movements were noted. A test for NMDA-R antibodies was performed, with detection in the patient's serum. She was then treated with intravenous immunoglobulin and methylprednisolone. After a 5-day course, she showed little improvement, when a transvaginal ultrasonography revealed a 9-mm echogenic focus in the right ovary. A chest/abdomen/

pelvis computed tomographic scan was obtained to exclude any extra-adnexal masses, and none were found. At this time, she began a course of rituximab.

Because of the small amount of the suspected dermoid tissue and the inability to accurately identify the cyst in laparoscopy, a laparoscopic right salpingo-oophorectomy was performed to ensure complete removal of the lesion due to the grave implications of incomplete removal of the tumor in this severe clinical condition. The procedure was uncomplicated, and histopathology of the ovary confirmed the presence of a mature cystic teratoma (**Figure 1**). Focal mature glial tissue was present in the specimen, and no analysis for NMDA-R expression in the specimen was performed.

The patient recovered well after surgery, was extubated on postoperative day 1, and was transferred from the ICU to the medical unit 8 days later. After an extended inpa-



Figure 1. Right ovary and fallopian tube, laparoscopically resected. **(A)** Right ovary and tube, removed intact. **(B)** Right ovary dissected, a tiny (9-mm) dermoid tumor is apparent in the right ovary (arrow).

tient stay, she was discharged to community rehabilitation services.

At outpatient review 8 weeks after surgery, the patient had returned to her baseline cognitive function, with the exception of ongoing headaches and lethargy.

DISCUSSION

Encephalitis due to NMDA-R antibodies was first described in 2007.¹ More than 500 cases have been reported in the literature. The first cases described were of women with ovarian dermoid tumors. This syndrome was later found to be associated with mediastinal teratomas, sex cord-stromal tumors, small-cell lung cancer, and testicular teratomas.² Dalmau et al² published the largest case series thus far, which included 100 patients (91 females and 9 males) with NMDA-R antibody encephalitis. Ovarian teratoma was the most prevalent tumor associated with the syndrome and was diagnosed in 56 females (62%; 56/91); 41% of the patients did not have an identifiable tumor.² Microscopic analysis of ovarian teratomas confirmed the presence of central nervous system (CNS) tissue, with NMDA-R expressed in 25 tumors that were further analyzed. Some dermoids, however, did not contain any CNS tissue. Its absence could be explained by the common neuroectodermal origin of cutaneous and CNS tissues, which may share some identical epitopes.³ An immune-mediated mechanism most likely underlies this syndrome. Antibodies formed against neoplastic cells cross-react with NMDA-Rs that are located at the surface of neurons, causing their destruction or down-regulation and impaired glutamatergic neurotransmission.² In the normal state, NMDA-Rs are found throughout the CNS, mediating a critical role in synaptic transmission and plasticity. In patients with anti-NMDA-R encephalitis, these antibodies cause less intense reactivity in the forebrain, basal ganglia, spinal cord, and cerebellum.^{2,4} Thus, antibodies may preferentially affect areas responsible for memory, personality, movement, and autonomic control. These patients may present with personality changes, confusion, seizures, or coma and can sometimes have arrhythmias and asystole.⁵ Laboratory identification of NMDA-R antibodies can lead to an accurate diagnosis of the clinical syndrome.

Anti-NMDA-R encephalitis is an underrecognized syndrome. It was retrospectively diagnosed in 86% (6/7) of patients treated in a single-center ICU with a diagnosis of encephalitis of unknown origin.⁶ Iizuka et al⁷ reported that anti-NMDA-R encephalitis and acute juvenile female nonherpetic encephalitis are the same. The number of cases of missed anti-NMDA-R encephalitis that have been

misdiagnosed and treated as psychiatric conditions remains unknown.

The diagnosis should be considered in the differential of all patients, especially women, who present with rapidly progressing confusion, psychosis, or movement disorders. The co-occurrence of seizures early in the illness course should raise suspicion of this syndrome. Complex and generalized seizures are reported in most cases (76% in the largest case series).² Imaging of the ovaries or testes is necessary, as there is a correlation between swift removal of the tumor and improved prognosis and decreased recurrence.² The choice of surgical procedure is still undetermined; some surgeons suggest that cystectomy is as effective as oophorectomy in selected cases.^{3,8}

The size of the dermoid tumor is not a factor in the pathogenesis of this syndrome; some of the dermoids excised have been as small as 1 cm² or smaller, such as in our case.

Given that laboratory testing and isolation of NMDA-R antibodies are diagnostic of the syndrome, it could be useful for neurologists and psychiatrists to perform early NMDA-R antibody testing in women with a presentation similar to our patient's and a negative MRI. Empiric treatment includes the use of intravenous corticosteroids, progressing to plasma exchange, intravenous immunoglobulin, or both. Surgical excision should be considered in all patients with a suspected tumor. The removal of the tumor "antigen" precedes a reduction in antibody titers² and offers the best chance of cure in affected patients.^{1,2,9}

Timely diagnosis and treatment of this syndrome allows for a good prognosis. Day et al¹⁰ reviewed the literature and found that 75% of patient recovered with minimal deficits. Mortality rates vary in different reports. Day et al described a case series of 3 patients with a mortality rate of 100%; others have quoted mortality rates between 0 and 25%.^{2,7,11,12}

Naoura et al³ have raised the option of systematic screening for NMDA-R antibodies in women with teratomas, due to the variability in severity and presentation of this syndrome. However, because in many cases the test is performed in CSF, necessitating a lumbar puncture, routine testing seems disproportionate to the rarity of the condition. Moreover, a similar clinical syndrome of encephalitis has recently been described in 22 patients by Höftberger et al.¹³ Those patients did not have NMDA-R antibodies; their clinical symptoms were caused by antibodies to the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA-R). Fourteen (63%) had an associated

tumor, of which 2 (9%) were ovarian teratomas. This report raises the possibility that ovarian teratomas are contributory to the pathogenesis of encephalitis, even if the serology screen is negative.

In conclusion, autoimmune encephalitis is a complex and life-threatening condition. Patients usually present to the gynecologist at a late stage subsequent to referral from ICU, neurology, psychiatry, or other departments after the diagnosis has been made or suspected. Knowledge of this syndrome and quick surgical removal of the ovarian teratoma, however small it may be, can be a significant factor in reducing morbidity and mortality. This syndrome, although very rare, may be incorporated in the counseling of women regarding resection of the ovarian teratoma.

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