Case Report

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More than teen angst: A case of ovarian teratoma presenting as anti-N-methyl-d-aspartate receptor encephalitis

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Abstract:

A 17-year-old nulligravid presented with labile mood, insomnia, and hyper-productive speech for 2 days, which progressed to seizures. Cerebrospinal fluid was positive for anti-N-methyl-d-aspartate (NMDA) receptor antibodies. Despite immunotherapy and seizure prophylaxis, she had status epilepticus and rapid decrease in sensorium. She was placed on ventilatory support and was admitted in the intensive care unit. On the 44th hospital day, an incidental finding of an ovarian teratoma was seen on abdominal computed tomography scan. She underwent right salpingo-oophorectomy, which revealed an immature teratoma. The absence of an intensive care admission and prompt surgery and immunotherapy are known predictors of good outcome in anti-NMDA receptor (NMDAR) encephalitis, with improvement seen in 80% of patients. Because most ovarian teratomas are only diagnosed as an incidental finding, anti-NMDAR encephalitis with a concurrent ovarian teratoma should be suspected in young females presenting with sudden-onset neuropsychiatric symptoms, to provide the timely intervention necessary for a good prognosis.

Keywords:

Encephalitis, immunotherapy, N-Methyl-D-Aspartate, seizure, teratoma

Introduction

Ovarian teratomas are one of the most common gynecologic neoplasms among pediatric and adolescent patients. Typically, patients with teratomas present with an adnexal mass or abdominal pain.[1] However, in recent years, there have been case reports of teratomas associated with patients having sudden onset neuropsychiatric symptoms. In 2005, the link behind the peculiar symptomatology was discovered when Dalmau *et al.* found anti-N-methyl-d-aspartate receptor (NMDAR) antibodies in the patients' cerebrospinal fluid (CSF).[2] The disease was then called anti-NMDAR encephalitis and was described to be a rare form of autoimmune paraneoplastic encephalitis.

In the initial study by Dalmau *et al.*,[2] 14 women aged 14–44 years old presented with neuropsychiatric symptoms such as seizures, dyskinesia, and decreased level of consciousness often necessitating ventilatory support. Of these women, 13 were incidentally found to have ovarian teratomas while one had a mediastinal teratoma. Thirteen of these women also presented with neuropsychiatric symptoms 3 weeks to 4 months before the diagnosis of teratoma on imaging studies while the other was previously diagnosed with an ovarian cyst. CSF from all 14 of the patients contained antibodies NMDA receptors, which are preferentially expressed in the hippocampus.

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Since its discovery, treatment of anti-NMDAR encephalitis has been focused on immunotherapy and removal of the tumor producing anti-NMDAR antibodies, most commonly, a teratoma.[3] In a study done in 2013, approximately 80% of patients improved or recovered after immunotherapy and surgery. In the same study, early intervention and the absence of intensive care admission were identified as predictors of good outcome.[4] However, diagnosis of anti-NMDAR encephalitis is proved difficult by its nonspecific presentation, commonly attributed to psychiatric causes. In common practice, it is not until neurologic symptoms arise and other possible causes such as infection, infarction, or mass effects are ruled out, would autoimmune encephalitis be entertained – a course of practice that is predictable, given that anti-NMDAR encephalitis was only discovered 16 years ago.

With those in mind, the aim of this case report is to empower a physician with the knowledge on (1) the typical presentation and patient profile of a patient with anti-NMDAR encephalitis caused by an ovarian teratoma, (2) the diagnostics and treatment options for these patients, and (3) their prognosis, focusing on psychiatric and neurologic symptoms postsurgery.

Case Report

This is a case of a 17-year-old nulligravid, off-cycle, obese class II, with a body mass index (BMI) of 30.1, with no other comorbidities, who came in with a 2-day history of auditory hallucinations, labile mood, insomnia, and hyper-productive speech. On the day of admission, she had generalized tonic-clonic seizures which prompted consult in the emergency room and subsequent admission. Cranial magnetic resonance imaging was negative for intracranial mass, bleed, or ischemia. CSF was negative for signs of infection. Due to the high index of suspicion for anti-NMDAR encephalitis, CSF was tested for and was found to be positive for anti-NMDAR antibodies. The patient was started on methylprednisolone and immunoglobulins for immunosuppression and midazolam for seizure prophylaxis.

Initially, the patient was responding well to treatment, with no seizure recurrence. On the fifth hospital day, the patient had status epilepticus, with seizures described as twitching of the face and hypersalivation, later progressing to tonic-clonic movements of the bilateral upper and lower extremities, typically lasting for a few seconds per episode. Whole abdominal ultrasound was done which turned out negative for the presence of ovarian teratoma. She was then transferred to the intensive care unit where she was placed on ventilatory support.

In the intensive care unit, her blood pressure was unstable, fluctuating from hypertension to hypotension, which at times, necessitated vasopressors. Her sensorium decreased rapidly from Glasgow Coma Score (GCS) of 15–9 (E = 4, V = 1, M = 4). There was no seizure recurrence, however, the patient developed automatisms such as oral dyskinesia and had persistent hyperthermia as high as 40°C.

Due to her prolonged mechanical ventilation, she eventually developed hospital-acquired pneumonia and was started on broad-spectrum antibiotics. She was unable to tolerate weaning off of ventilatory support and on the 35th hospital day, tracheostomy was done.

On 44th hospital day, whole abdominal computed tomography (CT) scan was done to once again, rule out an ovarian teratoma, which showed a well-defined, heterogeneously enhancing, ovoid, mixed solid, and cystic mass in the right adnexa measuring 5.6 cm × 5.2 cm × 4.1 cm, suggestive of teratoma [Figure 1]. She was then referred to gynecology service for the surgical removal of the aforementioned mass. Transrectal ultrasound was done which showed an ovarian cyst, right, measuring 4.26 cm × 4.71 cm × 6.71 cm, with a volume of 70.41 ml, with no color on flow mapping, suggestive of a dermoid cyst.

Surgical planning was immediately discussed, with the goal of conducting the tumor removal with the least amount of time, due to the patient's unstable blood pressure and persistent hyperthermia. Since insufflation of the abdominal cavity through a laparoscopic procedure would have caused hypotension, it was then ruled out. The plan was to do an oophorocystectomy or a salpingo-oophorectomy under laparotomy. The patient was eventually cleared to undergo surgery after the

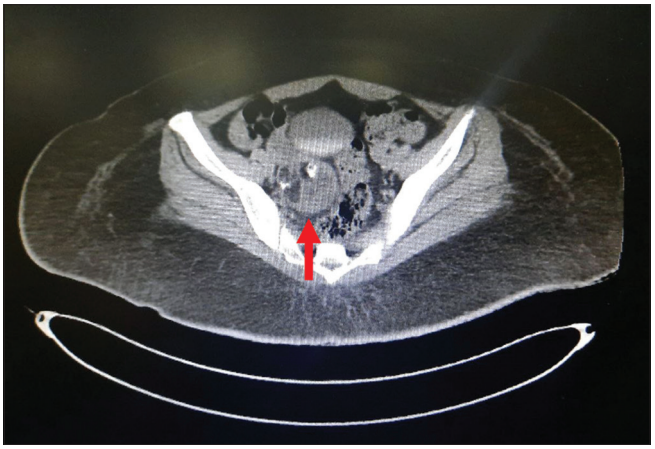

Figure 1: Abdominal computed tomography scan result: a well-defined, heterogeneously enhancing, ovoid, mixed solid, and cystic mass in the right adnexa (arrow) measuring 5.6 cm × 5.2 cm × 4.1 cm, with coarse calcific and fat-attenuating components detected within the lesion, suggestive of teratoma

initiation of plasmapheresis, which would be completed after the procedure.

On the 63rd hospital day, she underwent exploratory laparotomy with right salpingo-oophorectomy. Intraoperatively, the right ovary was enlarged to 8.2 × 6.3 × 3.3, with a smooth pearl white external surface with fine vascularities [Figure 2]. On cut section, it was thin-walled and multiloculated, with soft sebaceous tissue interspersed with solid calcific nodules. The uterus, left ovary and left fallopian tube, and right fallopian appeared grossly normal. Since the intraoperative finding was consistent with a benign dermoid cyst, the patient was immediately closed after hemostasis and was transferred back to the intensive care unit. On histopathologic review, the tumor showed high grade immature teratoma [Figure 3]. Postoperatively, there was no improvement in her GCS, which remained at 9 (E = 4, V = 1, M = 4). There was still no seizure recurrence and her automatisms persisted. Her febrile episodes decreased. However, she still could not tolerate weaning off of mechanical ventilation.

On the 108th hospital day, she was then discharged stable, on mechanical ventilation.

Discussion

Clinical presentation of teratomas

Germ cell tumors are the second most common neoplasms of the ovary, accounting for 20%–25% of all ovarian tumors. There are three main types of ovarian germ cell tumors: mature teratoma (dermoid cyst), immature teratoma, and dysgerminoma.[5]

Approximately 20% of women with teratomas are asymptomatic at the time of discovery. Around 5%–10% may experience acute abdominal pain when there is torsion or for around 3% of patient, when there is rupture, and fat is spilled in the peritoneal cavity, causing peritonitis.[5]

Before the work-up done due to the diagnosis of anti-NMDAR encephalitis, the patient was asymptomatic, with no history or palpable abdominal masses or abdominal pain.

Clinical presentation of anti-NMDAR encephalitis

For about 2 weeks before the onset of neuropsychiatric symptoms, 70% of patients with anti-NMDAR encephalitis typically experience a prodrome of headache, fever, nausea, vomiting, diarrhea, or upper respiratory symptoms.[6] This is followed by psychiatric symptoms such as anxiety, insomnia, fear, grandiose delusions, hyper-religiosity, mania, and paranoia, which then progresses to rapid disintegration of language, from reduction of verbal output and echolalia to frank mutism.[6] Patients then experience a decrease in sensorium, abnormal movements, and autonomic manifestations. Abnormal movements usually manifest as oro-lingual-facial dyskinesia and limb and trunk choreoathetosis. Autonomic dysfunction includes hyperthermia, tachycardia, hypersalivation, hypertension, bradycardia, hypotension, urinary incontinence, and erectile dysfunction. Hypoventilation is typically described as central, and as a result, these patients could not be weaned off ventilatory support. Seizures are also seen among anti-NDMAR encephalitis patients, which could mimic the expected abnormal movements of these patients, leading to under-recognition of seizure episodes, causing status epilepticus. At this stage of the disease process, patients are usually admitted to intensive care units for management.

This progression of symptoms was seen in clinical presentation of the patient. Although there was no note of having signs of the prodrome, she presented with auditory hallucinations, mood lability, insomnia,

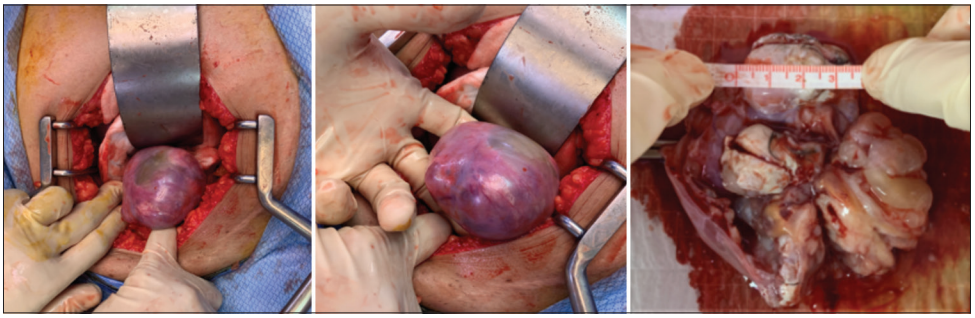

Figure 2: Intraoperative findings: intraoperatively, the right ovary was enlarged to 8.2 × 6.3 × 3.3, with a smooth pearl white external surface with fine vascularities [Figure 2]. On cut section, it was thin-walled and multiloculated. One locule measured 3.2 × 2.6 × 2.2 cm, on cut-section contained soft sebaceous tissue interspersed with solid calcific nodules and exuded mucoid yellow fluid. Another locule measured 2.6 x 1.9 x 1.6 cm and contained soft, sebaceous tissue. Another locule measured 1.6 cm × 1.4 cm × 1.2 cm, contained soft, sebaceous tissue with tufts of hair. Another locule measured 4.6 cm × 2.9 cm × 2.5 cm, contained soft sebaceous tissue interspersed with solid components and exuded mucoid yellow fluid. Another locule measured 2.0 cm × 2.1 cm × 2.1 cm contained soft sebaceous tissue with solid components and exuded creamy white fluid. The right fallopian tube was red-tan, appeared grossly normal, and measured 5.1 cm × 0.6 cm. The uterus, left ovary, and left fallopian tube appeared grossly normal

and hyper-productive speech, which then progressed to seizure episodes and decrease in sensorium, which then prompted airway protection and intensive care admission. In the intensive care unit, she had orolabial dyskinesias, choreoathetosis, and autonomic instability manifesting as hyperthermia and blood pressure lability, which are all congruent with the typical presentation of anti-NMDAR encephalitis.

Epidemiology

In the local setting, the first documented case of anti-NMDAR encephalitis was seen in 2012 by Carpio *et al.*, when a 36-year-old female presented with behavioral change and seizures and was found to have an immature mesenteric teratoma, with serum and CSF both positive for anti-NMDAR antibodies.[7] The first reported case of anti-NMDAR encephalitis associated in an ovarian teratoma was in 2014 by Munoz *et al.*, with a 36-year-old nulligravid, who had good recovery after surgery and immunotherapy.[8]

The exact incidence of anti-NMDAR encephalitis is still unknown due to its rarity, but the estimated incidence is said of be 1.5/1,000,000 population.[3] 59% of the patients initially present with psychiatric symptoms. Because of the lack of awareness of this disease, 41% of these patients were first admitted in a psychiatric institution – causing a delay in treatment and emphasizing the need for physicians to be more familiar with the disease.[3]

Risk factors

Ovarian germ cell tumors such as teratomas usually present in young women around 10–30 years old. Around 70% of ovarian germ cell tumors are comprised of benign mature cystic teratoma. Malignant ovarian germ cell tumors are more commonly found among Pacific Islanders, Asians, and Hispanic women, compared to Caucasians.[9]

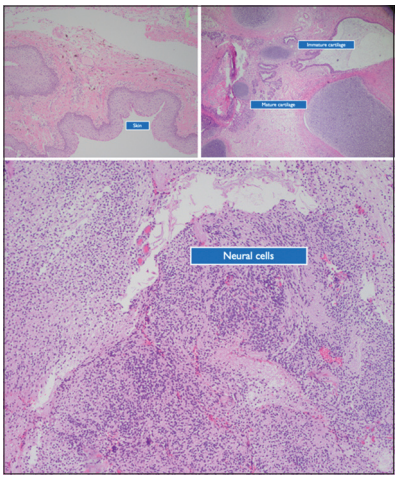

Figure 3: Histopathology findings concurrent with an immature teratoma, with skin, immature and mature cartilage, and neural cells

Patients with anti-NMDAR encephalitis are mostly female, with a female-to-male ratio of 8:2 and a median age of 21 (range: <1–85 years).[3] As of present, there are two confirmed triggers of anti-NMDAR encephalitis, mainly: tumors (mostly ovarian teratomas) and herpes simplex encephalitis.[3] These risk factors were all found in the patient.

Pathophysiology

Teratomas of those with anti-NMDAR encephalitis compared to those without were found to have a more abundant neuroglial component, and inflammatory cells, with an overrepresentation of B-cells, which were found to produce anti-NDMAR antibodies *in vivo*. As NMDA receptors are preferentially expressed in the hippocampus, a part of the limbic system, responsible for emotional control and memory, the overrepresentation of B cells and neuroglial tissue in the teratomas of these patients could point to the pathophysiology behind the disease.[3]

Diagnosis

In 2016, a Diagnostic Criteria for anti-NMDAR encephalitis were proposed and are summarized in Table 1.[3] In 2019, Dalmau *et al*. proposed the mnemonic "Search for NMDAR-A" to aid in the diagnosis, as seen in Table 2.[3] As of date, the definite diagnosis of anti-NMDAR encephalitis is dependent on the detection of IgG GluN1 antibodies in the serum and/or CSF.

On the other hand, diagnosis of ovarian teratomas is done through ultrasonography. Teratomas usually present with focal or diffuse hyperechoic components, areas of acoustic shadowing ("tip of the iceberg" sign), and echogenic lines and dots called the "dermoid mesh" or "dot-dash" sign. Combinations of these findings correspond to the hair and sebaceous material. A "Rokitansky nodule" or a hyperechoic component corresponding to calcified tissue such as a bone or a tooth may also be seen.[1]

In the patient's case, after the confirmation of anti-NMDAR antibodies in the CSF, a transabdominal ultrasound was done, which turned out negative for any form of pelvic masses. The finding of ovarian teratoma was only obtained though an abdominal CT scan on the 44th day of admission. A possible explanation for this course could be a limitation in the initial mode of imaging due to the patient's BMI or possibly, the teratoma at that time may have been microscopic, only growing big enough to be seen in the subsequent imaging. The latter scenario was also seen in another case, wherein a patient had a microscopic teratoma confirmed only after prophylactic oophorectomy.[3]

Management and Prognosis

Patients with teratomas are managed based on the size of the adnexal mass, age, and symptoms of the patient. Decision to do surgery on an asymptomatic patient will depend on the patient's age and size of the mass, which is summarized on Table 3. If the patient is presenting with signs of pressure or torsion, then immediate surgery is warranted.[10] Benign cystic teratomas do not recur once surgically removed. Immature teratomas, on the other hand, have a recurrence rate of 12%–25%, requiring adjuvant chemotherapy with bleomycin, etoposide, and cisplatin. Immature teratomas have a good prognosis, with a 90% 5-year survival rate.[5]

Management of patients with anti-NMDAR encephalitis is centered on immunotherapy, the first-line therapy being steroids, intravenous immunoglobulins, or plasmapheresis. Patients who do not improve after 4 weeks of administration of first-line therapy may be transitioned to second-line therapy of rituximab or cyclophosphamide. Those refractory to these treatment options may be offered third-line therapy composed of bortezomib or tocilizumab. Removal of tumor could also be done with approximately 80% of patients improved when surgery was partnered with immunotherapy. However, the said response is said to be associated with predictors of good outcome, namely: early intervention and the absence of intensive care.[3]

In this patient's case, despite immunotherapy and surgery, the patient's sensorium and functionality did not improve more than a month postsurgery, which could have been due to the absence of the predictors of good outcome in her case. This emphasizes the need for physicians to be able to rule out anti-NMDAR encephalitis and ovarian teratomas among young women presenting with the signs and symptoms discussed in this paper.

Summary

Patients with ovarian teratomas are usually asymptomatic, with abdominal pain only occurring as a consequence of either torsion or peritonitis. In recent years, there have been cases where young women present with sudden-onset neuropsychiatric symptoms, decrease in sensorium, seizures, and dyskinesia. It was only in 2005 when this disease entity was attributed to anti-NMDAR antibodies in the patients' serum or CSF. On further workup, these patients were found to have teratomas, which are hypothesized to be the source of anti-NMDAR antibodies. Due to this association, anti-NMDAR encephalitis was then considered to be a form of autoimmune paraneoplastic encephalitis. Treatment was centered on prompt diagnosis, immunotherapy, and removal of tumor, with a favorable prognosis depending heavily on the lack of intensive care admission and early intervention,

Table 1: Diagnostic criteria for anti-N-methyl-D-aspartate receptor encephalitis

Probable
Rapid onset (<3 months) of at least four of the six major groups of symptoms
Abnormal (psychiatric) behavior or cognitive dysfunction
Speech dysfunction (pressured speech, verbal reduction, or mutism)
Seizures
Movement disorder, dyskinesias, rigidity, or abnormal postures
Decreased level of consciousness
Autonomic dysfunction or central hypoventilation
And at least one of the laboratory studies
Abnormal EEG (focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brush)
CSF with pleocytosis or oligoclonal bands
Or three of the above groups of symptoms and identification of a systemic teratoma
Exclusion of recent history of herpes simplex virus encephalitis or Japanese B encephalitis, which might result in relapsing immune-mediated neurological symptom
Definite
One or more of the six major groups of symptoms and IgG GluN1 antibodies (antibody testing should include CSF); if only serum is available, confirmatory tests should be included (e.g., live neurons or tissue immunohistochemistry, in addition to a cell-based assay)
Exclusion of recent history of herpes simplex virus encephalitis or Japanese B encephalitis, which might result in relapsing immune-mediated neurological symptoms

EEG: Electroencephalogram, CSF: Cerebrospinal fluid

Table 2: "Search for anti-N-methyl-D-aspartate receptor"

S: Sleep dysfunction
E: Excitement, disinhibition, or manic behavior alternating with depressive behavior
A: Agitation or aggression
R: Rapid onset
C: Children and young adult predominance
H: History of psychiatric disease absent
F: Fluctuating catatonia
N: Negative and positive symptoms at presentation
M: Memory deficit
D: Decrease of verbal output or mutism
A: Antipsychotic intolerance
R: Rule out neuroleptic malignant syndrome

Table 3: Management of adnexal mass per size and age group

Age group	Surveillance[1]	Surgical (cm)
Premenarcheal	<10 cm	>10
Reproductive age	<5 cm=Expectant 5-7 cm=Annual surveillance	>7
Postmenopause	≤7 cm=3-6 months surveillance May decrease to annual surveillance if with no increase in size	>7

[1]Expectant as long as asymptomatic, tumor markers are normal and with benign features on imaging

with approximately 80% of patients improving with timely surgery and immunotherapy. Therefore, it is important to suspect anti-NMDAR encephalitis with a concurrent ovarian teratoma when presented with a case of a previously well young female coming in with signs and symptoms consistent with anti-NMDAR encephalitis. As of date, there is still limited data on the long-term sequelae and recurrence of anti-NMDAR encephalitis. Dermoid cysts or mature teratomas do not recur after surgical excision, whereas immature teratomas have a 90% 5-year survival rate once given the appropriate chemotherapy after surgical excision.

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Conflicts of interest

There are no conflicts of interest.

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