Case Report

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A diagnostic dilemma: Laparoscopic approach in treating ovarian teratoma-associated anti-N-methyl-D-aspartate receptor encephalitis

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Abstract:

A 24-year-old nulligravida who presented with seizures and behavioral changes with prodrome of flu-like symptoms was initially treated as a case of viral encephalitis. Neurologic diagnostic tests including electroencephalogram, cerebrospinal fluid analysis (CSF), and cranial magnetic resonance imaging were done and inconclusive. Patient's seizure attacks persisted and her neurologic status was deteriorating despite giving appropriate anti-epileptic medications, hence an autoimmune disease was highly considered. The CSF was positive for N-methyl-D-aspartate receptor antibodies. This prompted a search for an associated teratoma and revealed a diagnostic dilemma between presence of an ovarian new growth versus a normal enlarged ovary. Laparoscopy which is both diagnostic and therapeutic was utilized. This report highlights prompt recognition of a rare case and prevented its progression to a potentially fatal condition as resection of the tumor dramatically relieved the symptoms. The significance of minimally invasive surgery in managing this case, effect in fertility, and possible association with pelvic inflammatory disease are also discussed.

Keywords:

Laparoscopy, N-methyl-D-aspartate, receptors, teratoma

Introduction

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a rare, widely underdiagnosed, potentially lethal but reversible autoimmune disorder. It typically presents with neurologic and psychiatric symptoms in progressive stages often with no gynecologic symptoms. The correlation between an ovarian teratoma and encephalitis was first described in 1997. The case report described a 19-year-old Japanese girl presenting with convulsion and psychosis, and improved following tumor removal.[1] Interest in this disease grew, and in 2005, Dalmau first demonstrated antibodies against the NMDA receptor in these patients.[2]

A case series on more than 400 patients with NMDA receptor encephalitis found that at least 80% of patients are female and the mean age of presentation is at 18.5 years. Anti-NMDA receptor encephalitis has been reported to have a preponderance in Asian and Pacific Islanders, and an accompanying ovarian teratoma is more common among the Black race. It has

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been demonstrated recently that anti-NMDA receptor encephalitis may occur during pregnancy and can have good consequences for both the mother and the newborn.[3]

More than 500 cases have been published worldwide, but in the Philippines, only 2 previous studies have been published between the association of NMDA receptor encephalitis and an ovarian teratoma in 2018. This is the third case reported in the Philippines in 2018, and was successfully managed laparoscopically.

Case Report

A 24-year-old nulligravida was brought to the emergency room (ER) due to the first episode of seizure. The patient was apparently well until 3 weeks prior to admission when the patient was noted to have nonproductive cough and colds unrelieved by self-medicating with antitussives but no associated headache or fever. Symptom persisted until 2 weeks prior to admission, the patient started having episodes of difficulty in concentration and episodes of short-term memory loss but was still able to perform activities of daily living independently at this time. On the day of admission, the patient was rushed to the ER due to tonic-clonic seizures which lasted for around 60 s. This was followed by postictal confusion and lapses in memory. Complete blood count and cranial computed tomography scan were requested and all were unremarkable. She was advised admission for further investigation due to recurrence of the seizure. However, due to lack of room vacancy, she was transferred to another private tertiary hospital.

After transfer to another hospital, at the ER, the patient again developed tonic-clonic seizures. She was given diazepam 5 mg intravenous (IV). She was admitted and transferred to a regular room. Her attending neuropsychiatrist requested a lumbar puncture. Two days before the scheduled procedure, the patient was noted to be agitated, restless, with bizarre behavior like laughing out loud and throwing things all around the room. At this point, the attending physician was highly considering a viral encephalitis versus autoimmune-mediated encephalitis.

Lumbar puncture was done in the operating room under sedation. She was then started on IV antibiotic (ceftriaxone), antiviral (acyclovir), anticonvulsants (diazepam and valproic acid), and antipsychotic drug (olanzapine). Result of the cerebrospinal fluid (CSF) analysis showed leukocytosis with predominance of lymphocytes. There was no improvement in the patient's condition despite the medications. The patient still continued to have recurrence of seizures with the same characteristic and duration. Her anti-epileptic drugs were titrated accordingly. At this point, her attending physician was highly considering a paraneoplastic syndrome, hence whole abdominal ultrasound was done which showed a 6 cm × 6 cm complex right adnexal mass likely ovarian in origin. At this time, the relatives opted to transfer to a tertiary government hospital due to financial constraints.

Upon transfer to a government hospital, the patient was noted to have sustained eye opening, with regard but does not follow commands. Neurologic examination showed no focal neurologic deficit and meningeal signs. Medications were continued and titrated. Electroencephalogram was performed revealing a generalized slowing background with no epileptiform changes. Cranial magnetic resonance imaging (MRI) was done and was nonspecific. For the attending physician, a case of autoimmune encephalitis was considered, hence lumbar puncture was done again and was sent for anti-NMDA antibody titer (CSF and serum).

The patient was referred to gynecology service for evaluation of the whole abdominal ultrasound result taken from the previous hospital. The patient had no history of vaginal discharge, abdominal pain, changes in menstruation, or a palpable abdominal mass. On physical examination, she has a soft nontender abdomen. On internal examination, the cervix was firm, long, and closed with no cervical motion tenderness. The right adnexal mass measuring 6 cm × 5 cm was palpated and was freely movable and nontender. Transvaginal ultrasound [Figure 1] revealed a right ovarian new growth, right probably benign measuring 5.94 cm × 3.42 cm × 3.25 cm with multiple cystic spaces, cannot totally rule out an enlarged right ovary. The gynecology service suggested that there is still room for observation at this point. After 2 days, there were still episodes of recurrent seizures and increased episodes of restlessness and bizarre behavior. At this time, the result of the anti-NMDA receptor antibody titer CSF came back positive. This confirmed the diagnosis of anti-NMDA receptor encephalitis. IV immunoglobulin (IVIG) was then started.

The patient was referred back to the gynecology service for definitive management of the mass. The patient was scheduled for diagnostic laparoscopy with frozen section. Intraoperatively, there was a 6 cm × 4 cm × 4 cm ovarian mass on the right, with filmy perihepatic and periovarian violin string filmy adhesions (Fitz-Hugh–Curtis syndrome). Frozen section revealed a benign ovarian cyst with cartilaginous tissues, then proceeded with oophorectomy on the right with no cyst spillage noted. Post-operative diagnosis was G0 mature cystic teratoma, right; s/p laparoscopic right oophorectomy with frozen section; Anti-NMDA receptor encephalitis, and chronic pelvic inflammatory disease (PID). Medications were continued. Doxycycline was started to cover for the chronic PID. The patient's partner was also treated with ceftriaxone and doxycycline.

The patient's condition remained unchanged for 2 days postoperatively, until on the 3rd postoperative day when she started to become arousable by name-calling, had regard, was able to follow commands, and was able to recall remote memory. No recurrence of seizure was noted. There was rapid improvement and recovery of neurologic function. She was discharged on the 5th postoperative day.

Discussion

Encephalitis is an acute inflammatory process affecting the brain parenchyma presenting with various neurologic dysfunction. It has numerous etiologies, namely viral, bacterial, and seldomly autoimmune.[4] The patient initially had neurologic symptoms consistent with a viral encephalitis because of her history of flu-like symptoms, seizure, and changes in behavior, hence she was treated with antiviral and anti-seizure medications. However, the patient was unresponsive to various medications and was even deteriorating, hence a high index of suspicion for an autoimmune etiology was considered. The patient had memory disturbances, persistent seizures unresponsive to anti-epileptic drugs, and absence of fever which are all consistent with an autoimmune encephalitis.

Autoimmune encephalitis is a disorder wherein antibodies are directed against central nervous system proteins causing inflammation of certain brain regions presenting with neuropsychiatric symptoms. It can be grouped into two broad categories, paraneoplastic or nonparaneoplastic, based on the presence or absence of an underlying tumor, respectively. Anti-NMDA receptor encephalitis is one of the most common types of paraneoplastic autoimmune encephalitis commonly seen in young women and children and is usually associated with ovarian tumors like teratoma.[5] The index patient is a female in her reproductive years with a temporal profile of symptoms that fits that of an autoimmune encephalitis, hence a search for the presence of an ovarian tumor was done.

The pathophysiology of anti-NMDA encephalitis is intriguing and is still not fully understood at the moment. Several theories have been proposed. Day *et al*. hypothesized that the detection of neurons expressing the NMDA receptor within ovarian teratomas resected from patients with NMDA receptor encephalitis suggests that neural tissue may be vital to autoantibody formation and disease pathogenesis.[6] However, in our patient, there was no neural tissue seen on histopathology.

Peery *et al*. theorized that the presence of a tumor may not be necessary for development of anti-NMDA encephalitis since a small percentage of patients had no detectable tumor. Instead, the prodromal infection may act as the antigenic trigger for the initial expansion of anti-NMDA receptor-specific lymphocytes via molecular mimicry.[7] Another plausible reason of the absence of neural tissue in the patient's specimen is incomplete sampling. The cuts were largely spaced, hence there are many possible areas that may contain the neural elements that were not sampled.

Anti-NMDA antibodies are able to cross the blood–brain barrier and bind to NMDA receptors expressed in many regions of the brain. The binding causes internalization of those receptors leading to a decrease in numbers of NMDA receptors in the postsynaptic membrane. NMDA receptor–antibody complex results in the reduction of the inhibitory neurotransmitter in the postsynaptic membrane, causing the predominance of excitatory neurotransmitters.[8] This would explain the seizures, memory problems, and behavioral abnormities seen in patients with NMDA receptor encephalitis and also in our index case.

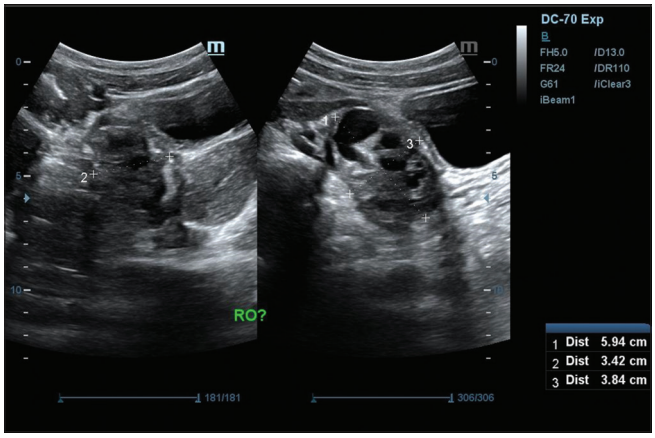

Figure 1: Transvaginal ultrasound showing a right ovarian new growth, probably benign measuring 5.94 cm × 3.42 cm × 3.25 cm with multiple cystic spaces, cannot totally rule out an enlarged right ovary

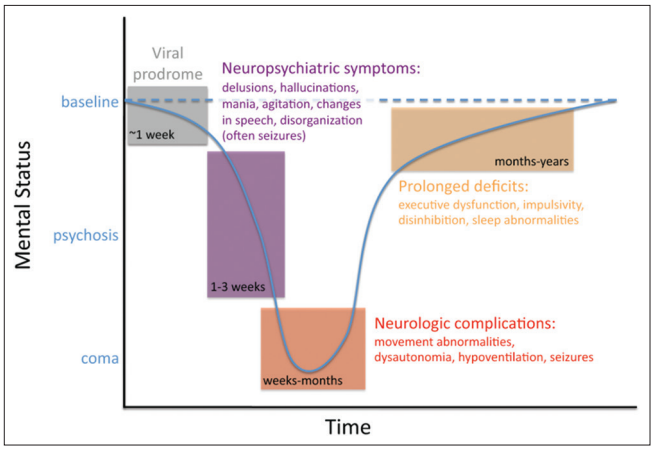

Figure 2: Phases of illness in patients with anti-NMDA encephalitis.

Anti-NMDA receptor encephalitis is a highly characteristic syndrome that appears to evolve and have distinct predictable phases of illness [Figure 2]. Foreseen knowledge of these stages can aid in early diagnosis to prevent irreversible complications and to initiate prompt management, since it can become life‑threatening in some untreated cases, with a mortality rate of up to 7%.[10] In our patient, the prodrome stage started with nonspecific viral-like illness with cough and colds, which are consistent with the spectrum of clinical characteristics of patients with anti-NMDA receptor encephalitis. The patient then proceeded to the stage of neuropsychiatric symptoms presented as first-onset seizure, changes in personality, and paranoid ideation following the usual course in these patients. The patient was caught at the neuropsychiatric stage wherein definitive management given at this stage halted the progression to the development of lethal and irreversible stage of neurologic complications presenting as the movement disorder, dysautonomia, and hypoventilation.

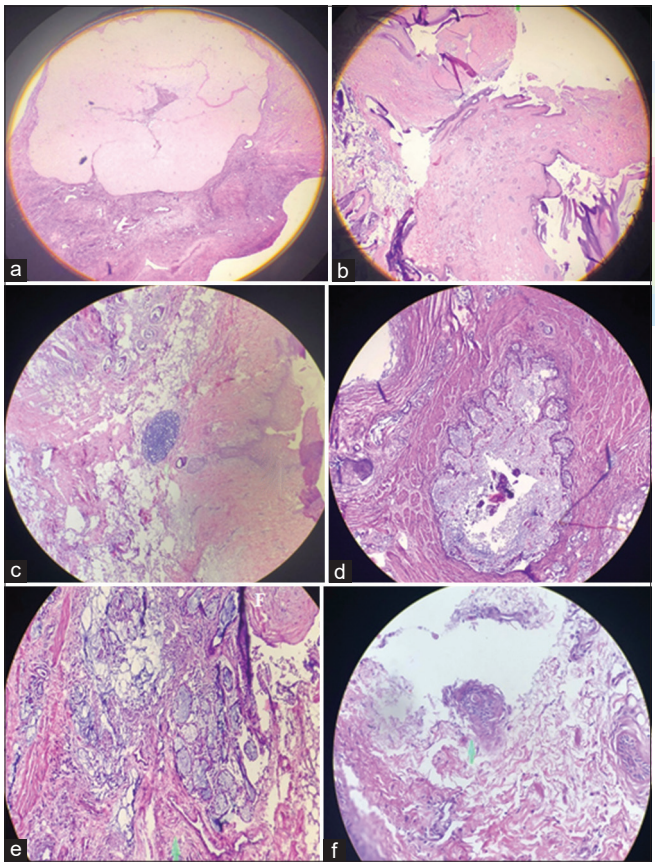

Figure 3: (a) Normal Ovarian tissue with Corpus albicans. (b) Skin. Keratinized stratified squamous epithelium (epidermis) and a fibroelastic connective tissue layer (dermis) with adnexal structure such as Sebaceous gland and Sweat glands. (c) Mature hyaline cartilage. (d) Respiratory type of epithelium. Pseudostratified columnar epithelium with Mucin secreting glands. (e) Intestinal type of epithelium with simple columnar epithelium. (f) Hair follicle The transvaginal ultrasound results [Figure 1] were equivocal, hence diagnostic laparoscopy with possible oophorectomy and frozen section was contemplated.

The patient was referred to gynecology service for the investigation of a possible ovarian mass given that anti-NMDA encephalitis is significantly associated with an ovarian mature teratoma in 57% of cases.[11] The transvaginal ultrasound results were equivocal, hence diagnostic laparoscopy with possible oophorectomy and frozen section was contemplated. Frozen section was utilized in this patient because anti-NMDA encephalitis may also be associated with an immature teratoma in a number of previous literatures.[1] If the mass turned out to be malignant, tumor staging can also be done during laparoscopy.

Laparoscopic oophorectomy was done in this case so as to ensure complete tumor removal since no normal ovarian tissue was seen on diagnostic laparoscopy. Laparoscopy over laparotomy has numerous advantages such as reduced febrile morbidity, lesser postoperative pain, and minimal postoperative complications. Such advantage was applied in our patient.

The final histopathology [Figure 3] revealed the presence of a mature cystic teratoma with mostly cartilaginous tissues, thus explaining the transvaginal ultrasound result which was not consistent with the classic sonographic findings of a teratoma. Teratomas generally contain fluid, fat, and hair particles which give characteristic ultrasound findings such as the dermoid plug sign and the tip of the iceberg sign, which are absent in our patient.[12]

Treatment options in cases of NMDA receptor encephalitis include methods to reduce antibody production such as immunotherapy and tumor resection

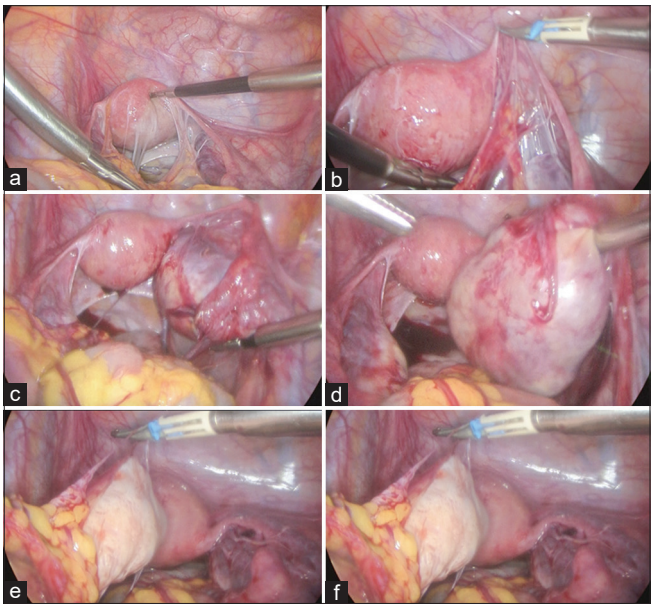

Figure 4: (a and b) Peri-ovarian adhesions. C and D. Right cystic ovary.

in cases of paraneoplastic anti-NMDA encephalitis. First-line immunotherapy consists of steroids and IVIG. It was shown to have enhanced effectiveness and speed of action when patients that have an underlying tumor undergo tumor resection.[13] Our patient underwent the first-line immunotherapy plus tumor resection as suggested. The patient manifested significant neurologic recovery within 3 days after the surgery.

The patient had an incidental finding of PID visualized on laparoscopy [Figure 4] as violin string adhesions in the perihepatic and periovarian areas. Sexually transmitted infections, such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, are commonly implicated in cases of PID. It was hypothesized that chlamydial proteins that mimic host self-proteins can contribute to initiation and maintenance of autoimmune diseases.[14] In the patient's case, the presence of her autoimmune disease makes her prone to develop fulminant pelvic inflammatory disease in the form of Fitz-Hugh–Curtis syndrome as seen on laparoscopy. The patient was also advised that the possible complications include tubal infertility, ectopic pregnancy, and chronic pelvic pain.

NMDA receptor encephalitis usually affects women of reproductive age, hence concerns for the patient's ovarian reserve preservation and future fertility is also a concern for the attending gynecologist. In our patient, right oophorectomy was done. Unilateral oophorectomy is known to cause reduced ovarian reserve because of the reduction of the total number of primordial follicles in their ovary and not a decrease of quality of the oocytes. In the patient's case, her age is at her advantage wherein her pool of primordial follicles is still theoretically high. The patient's history of pelvic inflammatory disease lowers her fertility in addition her surgery which is oophorectomy could further lower her fertility. A referral to reproductive endocrinology may be warranted in future.

It has been recommended that observation of ovarian tumor may be done in benign ovarian mass <5 cm. Because of the paucity of data regarding risk stratification of patients with small ovarian cyst or mature teratoma on the development of anti-NMDA encephalitis, aggressive removal of small tumors is still not warranted for its prevention. Furthermore, anti-NMDA encephalitis was also seen in cases without ovarian tumors and in inflammatory processes not requiring the presence of neural tissues from a benign teratoma.

Conclusion and Recommendation

Anti-NMDA receptor encephalitis is a type of autoimmune disease that warrants early diagnosis and prompt treatment to prevent irreversible complications and mortality. Despite its rarity, female patients showing symptoms similar to those of viral encephalitis, such as psychosis or seizures, should be worked up for the possibility of anti-NMDA encephalitis, especially when antiviral and anti-seizure medications do not provide good response. Identification of NMDA receptor antibodies confirms the diagnosis and should lead to the search for a tumor either by ultrasound or MRI. Laparoscopy, which is both diagnostic and therapeutic, may be performed for equivocal findings.

A multidisciplinary team involving a neurologist and a gynecologist is needed for its holistic management. Because of paucity of data on risk stratification and presence of various theories for the development of anti-NMDA encephalitis, aggressive removal of benign ovarian tumors or teratoma is not warranted for its prevention. Observation may still be contemplated in asymptomatic patients with benign ovarian mass or teratoma.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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