Recognizing the link between ovarian teratoma and autoimmune encephalitis: A case report of ovarian teratoma-associated anti-N-methyl-D-aspartate receptor encephalitis*

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ABSTRACT

A 36-year old nulligravid who initially presented with a one-week history of flu-like symptoms suddenly developed behavioral changes, agitation and irritability. Diagnostic tests were done and empiric treatment for viral encephalitis were initiated. Symptoms persisted with progressive unresponsiveness and episodes of seizure. Hypoventilation from dysautonomia required mechanical ventilation. Elevated levels of immunoglobulin on cerebrospinal fluid (CSF) and deterioration despite treatment raised suspicion for an autoimmune encephalitis. A referral to a gynecologist to rule out an ovarian focus was done. Ultrasound and biopsy established the presence of ovarian teratoma. The diagnosis of anti-N-methy-D-Aspartate receptor encephalitis was confirmed when the patient's serum and CSF tested positive for these antibodies. In addition, her CSF was also positive for anti-alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor (Anti-AMPAr) antibodies. In the Philippines, this was the second documented case of Anti-NMDAr encephalitis associated with ovarian teratoma and the first to have two antibodies present causing encephalitis.

Keywords: dermoid cyst, ovarian teratoma, anti-NMDAr encephalitis, anti-AMPAr encephalitis

INTRODUCTION

Germ cell tumors account for 20% of all ovarian neoplasms and comprise the second largest group of ovarian neoplasms next to surface epithelial tumors. It has a wide distribution and can be found in all ages from birth to menopause. In adults of reproductive age, the most common germ cell tumors are benign and 95% consist of dermoid cysts or mature cystic teratomas.[1] The term teratoma is a Greek word for "monstrous tumor" primarily because of its contents: hair, teeth, bone, neurons and sometimes eyes. The earliest documentation of teratomas dates from 600 to 900 BC from tablet clays that showed ways of predicting the future.[2] There were also ancient beliefs that these tumors were attributed to witchcraft curses and sexual misconduct with the evil. It was only until 1856 that teratomas were distinguished to contain the three germ cell layers: mesoderm, ectoderm and endoderm. Dermoid cysts are usually asymptomatic in 65% of cases and when symptoms present, it may include abdominal pain, mass or abnormal bleeding. There were reports that mature cystic teratomas may also cause autoimmune hemolytic anemia exhibiting progressive symptoms of anemia.[1] Excision of the tumor leads to the definitive treatment and resolution of this autoimmune type of anemia.[1] Furthermore, there is an increasing trend of cases reported about dermoid cysts being linked with another autoimmune disease entity now known as anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. Proper recognition of this link is therefore important not only to the neurologist but to the gynecologists as well. Appropriate management is prompt removal of the tumor. This is known to be curative. Timing is crucial in the recovery of patients with this type of encephalitis. Herein, we present a case of anti-NMDAR encephalitis associated with a small ovarian teratoma.

CASE REPORT

A previously healthy 36-year old, single, nulligravid from Ilocos Sur was admitted for the first time at a local tertiary hospital due to behavioral changes. She had no known co-morbidities and no previous hospitalizations. The complaint started with a one week history of flu-like symptoms presenting with colds, undocumented fever and headache. These were partially relieved with intake of paracetamol. Symptoms, however, progressed to behavioral changes characterized as agitation, irritability and disorientation to person. The initial impression was bacterial versus viral encephalitis. Work up and empiric treatment with ceftriaxone and acyclovir were given. Symptoms did not improve after two hospital days, hence, the decision to transfer to a bigger hospital for further management was made. Upon admission, she was drowsy but with spontaneous eye opening, with preferential upward gaze, no regard, does not follow command, with

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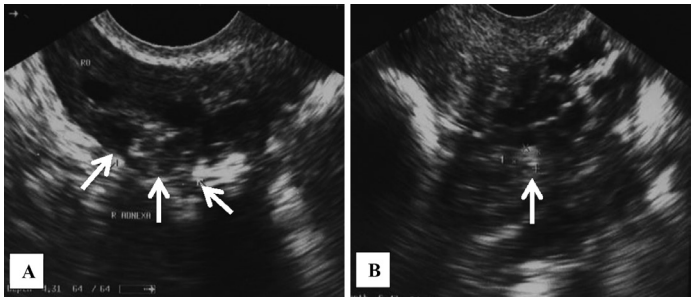

Figure 1. Ultrasound findings of the ovarian cysts: (A.) Antero-posterior view of the right ovary. At the superomedial pole of the right ovary is a cystic lesion measuring 2.2 x 2.1 x 1.7 cm containing low level echoes and two (2) brightly echogenic foci, medially measuring 1.4 x 1.0 x 0.9 cm and laterally measuring 0.6 x 0.5 cm (white arrows). (B.) Antero-posterior view of the left ovary showing a brightly central echogenic focus measuring 0.6 x 0.5 cm (white arrow).

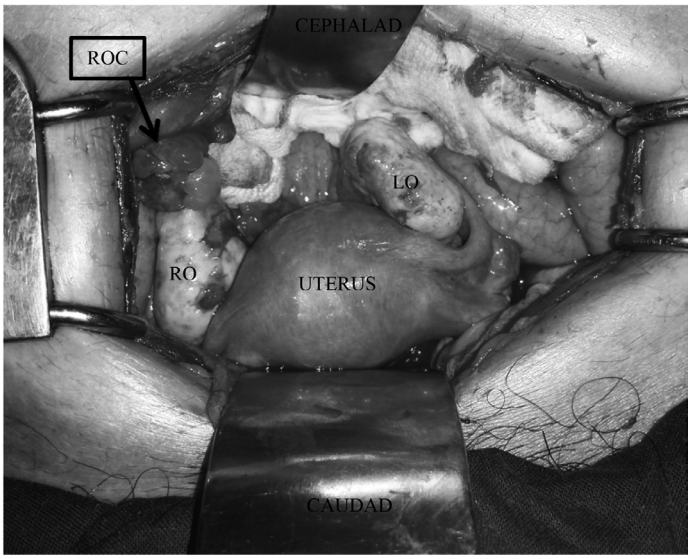

Figure 2. Intraoperative findings: superolateral to the right ovary is a 2.0 x 2.0 x 2.0 cm irregular, yellow tan, soft mass. The uterus, left ovary and bilateral fallopian tubes were grossly normal. (ROC = right ovarian cyst, RO = right ovary, LO = left ovary)

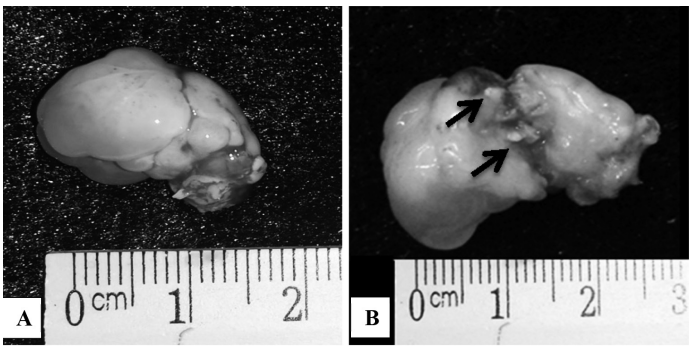

Figure 3. Right ovariancyst. (A) The right ovarian cyst measured 1.5 x 2.0 x 1.5 cm irregular, yellow tan, soft mass. (B) Cut section showing minute cartilage-like spicules (black arrows).

occasional groans, and not in cardio respiratory distress. Glasgow coma scale was 11 (eye opening 4, response to voice 2, motor 5) with no sensory deficits. However, on the first hospital day, she developed generalized tonic-clonic seizures. On further work-up, CSF studies revealed non-specific lymphocytosis, electroencephalogram (EEG), cranial computed tomography (CT) scan and magnetic resonance imaging (MRI) were also non-specific. On the 6th hospital day, she had autonomic instability characterized by intermittent hypotension, bradycardia, hypoventilation and desaturation, prompting intubation and mechanical ventilation. During intubation, she had cardiac arrest due to hypoxia but was resuscitated after two minutes. Referral to Obstetrics and Gynecology Service was done for investigation of an ovarian tumor. The sonographic findings were suggestive of dermoid foci in both ovaries (Figure 1). Issues concerning removal of both ovaries to prevent future relapse versus conservative oophorocystectomy to preserve fertility were discussed in a multidisciplinary meeting together with the family. On the 22nd hospital day, an exploratory laparotomy, right oophorocystectomy was performed upon consent of the family. Intraoperatively, there was a 1.5 x 2.0 x 1.5 cm irregular, yellow tan, soft mass superolateral to the right ovary (Figure 2). On cut section, it revealed soft, yellow, fatty tissues with minute cartilage-like material (Figure 3). Histopathology of the right ovarian mass showed cells from the three germ cell layers with mature brain tissue (Figure 4), layers of the epidermis, adipose tissue, gastrointestinal and respiratory epithelium, and chondrocytes (Figures 5A - 5F). The diagnosis of anti-NMDAr encephalitis was later confirmed when the result of serum and CSF studies sent to Spain revealed the presence of Anti-NMDAr antibodies. In addition, her CSF also had elevated titers of anti-alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor (Anti-AMPAr) antibodies. Post-operative course was unremarkable but no abrupt improvement was noted. She subsequently received five cycles of intravenous immunoglobulin. Partial improvement of seizures and orofacial dyskinesia was noted but patient remained unconscious. As a consequence, second line immunotherapy was given in the form of rituximab and cyclophosphamide. The presence of other tumors that may provoke production of the anti-AMPAr antibodies were also investigated but no other tumors were documented. After 135 hospital days, the family opted to bring the patient home. She was discharged with instructions for home care and regular visit to the provincial hospital where treatment of infections and immunotherapy can be continued. No recurrence of ovarian new growth was found on repeat pelvic ultrasound. Despite temporary improvements of dyskinesia, she was bedridden and

Figure 4. High power magnification (HPM) of a section in the right ovarian cyst showing neural differentiation of a mature brain tissue, with neurons (red arrows) and oligodendrocytes (black arrows).

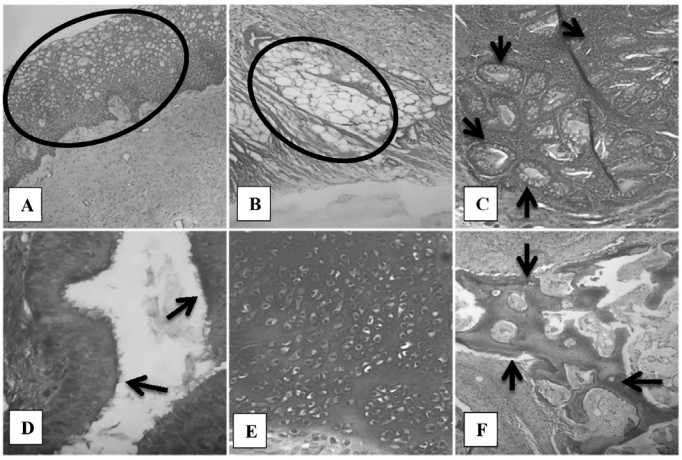

Figure 5. Photomicrographs of other cell types in the right ovarian mass: (A) HPM: layers of the epidermis which is a derivative of the ectoderm. (B) Low power magnification (LPM): adipose tissue (black circle) in the center of a fibrous stroma. (C) LPM: glandular differentiation, similar to the gastrointestinal epithelium (black arrows). (D) HPM: pseudostratified epithelium with ciliated borders, a histologic picture of a normal mature respiratory epithelium (black arrows). (E) HPM: clustered chondrocytes. (F) LPM: osseous differentiation. The irregular dark-staining amorphous matrix is bone with mesenchymal cells in the background (black arrows).

remained in a non-regard state. In due course, she expired from cardiorespiratory failure on the 28th day of April 2016.

CASE DISCUSSION

Epidemiology

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis was first recognized in 2005 when Dr. Joseph Dalmau and colleagues from the Department of Neurology in Pennsylvania wrote a series of papers supporting the connection of an ovarian teratoma and the activation of antibodies to NMDA receptors in the hippocampus. Since the publication of their work at the Annals of Neurology, there is an increased number of case reports published in journals of neurology and psychiatry but only 11% are published in obstetrics-gynecology journals.[3] This just shows that this pathological association has been under diagnosed and not reported among gynaecologists. Because of their initial symptoms, patients will most likely consult a neurologist or a psychiatrist before being referred to a gynecologist. In a systematic review of case reports by Acien *et al*, 174 cases of anti-NMDAr encephalitis caused by ovarian teratoma have been evaluated and studied. The mean age of patients reported with mature teratoma is 23.9 + 7.9 years with a median age of 24-years old.[3] Despite this, the age range may span from 20 months old to 84-years old, suggesting that the case may be diagnosed in all age groups.[4] The distribution of cases worldwide was uneven which could be explained by unreported cases. The variations in development of health care level and advancement of technology in terms of diagnostic imaging and screening may have affected the distribution of these cases. The incidence is almost similar in North America and Asia accounting for 30% and 29.5% of reported cases, respectively.[3] The greatest number of reported cases in Asia was in Japan accounting for 75% or 38 documented case reports. In the Philippine Journal of Obstetrics and Gynecology, there was a case reported by Munoz, *et al*., 32-year old nulligravid with classic presentation of anti-NMDAR encephalitis had good response after removal of tumor and administration of immunoglobulins.[5] In some cases, the teratoma was occult and was found microscopically only after oophorectomy or at autopsy.[3] Among these reported cases, 57% were associated with a mature teratoma while 16.7 % were associated with an immature teratoma.

Pathophysiology

It was theorized that the presence of neural tissues in dermoid cysts stimulates the body's immune system to produce autoantibodies against the NMDA receptors found throughout the brain, particularly in the hippocampus. Depletion of these receptors leads to reduced gamma-amminobutyric acid (GABA) in the neurons thus shutting down the inhibitory effects of glutamate release which would explain the neurologic and psychological

manifestations over time. The association was supported with the following observations: (1) presence of leukocytic infiltrates in areas of teratomas with neural tissue, (2) expression of NMDA receptor in the tissues of teratoma, (3) elevated titers of anti-NMDAR antibodies in serum and CSF, (4) the affected areas of the brain expresses the NMDA receptor (limbic and forebrain), and (5) treatment modalities that decreases the antibodies (immunotherapy or removal of teratoma) resulted to improvement of the set of symptoms.[6] Among these observations, the index case had 4 out of 5 findings. The expression of NMDA receptor in the ovarian teratoma was not investigated due to unavailability of the immunologic testing in our setting.

Clinical Presentation

The clinical presentation of anti-NMDAR encephalitis would often lead to an initial impression of psychosis or neurologic infection. The cascade of symptoms was grouped into five phases by Iizuka et al: prodromal, psychotic, unresponsive, hyperkinetic and recovery phase.[7] It begins with the prodromal phase in 90% of cases with symptoms of fever, malaise, headache, diarrhea, nausea or vomiting. This will be followed by the psychotic or seizure phase which is described by behavioral changes and emotional disturbances including depression, fear, hallucinations and delusions. Generalized tonic-clonic seizures were also exhibited. Next is the unresponsive phase, the patient will have involuntary movement, mutism, memory loss, inappropriate grimace and may no longer respond to verbal commands. The patient will appear as if in a state of catatonia. The hyperkinetic phase will then follow which will have symptoms of autonomic dysregulation such as hypo or hypertension, central hypoventilation, bradycardia, hypo or hyperthermia, and hypersalivation. Involuntary movements are also exaggerated and the patient will start to exhibit extrapyramidal signs such as orofacial dyskinesia, lipsmacking, clenching of teeth, mastication, choreiform movements, myoclonus and dystonia. Upon initiation of treatment, the recovery phase will follow and is a reversal of the previous symptoms described. This may range from 1 to 14 months but may take as long as 3 years or even longer in some cases.[3] In our case, the patient was already managed during the hyperkinetic phase. The course of her symptoms had a classic progression starting from the prodrome of headache, colds and fever. Notably, our case also presented with behavioral changes such as irritability and agitation, such that she was initially thought to have work-related depression and anxiety. The symptoms that followed led to a more thorough investigation.

Diagnosis

The diagnosis can be challenging and important as early recognition and treatment have favorable outcome. It requires comprehensive history, physical examination and tests that will rule out other causes of encephalitis including cerebrospinal fluid analysis, cranial CT scan or MRI and EEG. The CSF findings may include moderate lymphocytic pleocytosis, proteinuria and presence of immunoglobulins in 60% of cases.[8] Cranial MRI may be non-specific and was found to be unremarkable in 50% of cases.[9] Findings on the EEG are abnormal and may exhibit non-specific disorganized activity. The presence of a tumor, particularly a teratoma, will most likely boost the consideration of this kind of encephalitis. However, absence of an ovarian mass does not essentially rule out the disease because there have been cases of occult teratoma on autopsy findings of some case reports. The definitive diagnosis of anti-NMDAR encephalitis is based on the identification of NMDA receptor antibodies in serum or CSF. Unfortunately, access to this laboratory test is not available in the Philippines and samples were mandated to be sent overseas to reach Spain thru communication with Dr. Dalmau's team. Dr. Joseph Dalmau is also the current senior investigator and director of the laboratory for the study of the pathogenesis of immune-mediated neuronal disorders in University of Barcelona, Spain.

Management

At present, there is no existing standard modality of treatment for encephalitis induced by ovarian teratoma. Management of these cases require a multidisciplinary approach. If the encephalitis is found to be induced by ovarian teratoma, the mainstay of management involves early tumor resection along with immunosuppression as these leads to better outcomes and rapid recovery.[3] In patients without any tumor identified, the first line immunotherapy will often be intravenous methylprednisolone followed by intravenous immunoglobulin (IVIg) or plasmapheresis. The second line immunotherapy includes rituximab, cyclophosphamide or azathioprine. Unfortunately, literature supporting their use is scarce and is indicated only for cases with delayed diagnosis or no response after 10 days of the first line immunotherapy.[10] The abovementioned modes of treatment were received by the index case. She had first (methylprednisolone and IV immunoglobulin) and second line immunotherapy (rituximab and cyclophosphamide) after surgical removal of the right ovarian mass. Despite all these interventions, improvement was minimal or none at all. In the author's present viewpoint, unanswered questions still come to play. If we chose to do bilateral oophorectomy, will there be any marked improvement observed? Was recovery prolonged because of the mere presence of another antibody found? There was a case report of anti-AMPAr encephalitis which was also unresponsive to immunotherapy, she had negative

tumor on imaging but oophorectomy was still done. As predicted, occult teratoma was documented on the histopathology and this patient recovered despite a delay in surgical treatment.[6] The matter on how far should we go removing an ovarian focus particularly if there was no response to treatment must be discussed. It was initially presumed best to remove both ovaries knowing that the removal of all the sources of antibodies in its entirety leads to an improved outcome especially in patients refractory to immunotherapy. It may also prevent future relapse or recurrences which may be seen in 25% of cases that recovered.[3] However, as obstetrician-gynecologists, we should minimize unnecessary oophorectomies that may render the patient in an early menopausal state assuming that these patients will eventually recover from this disabling condition. The team and family agreed to an oophorocystectomy, in high hopes that she will soon recover. The left ovarian focus was very small to be seen grossly and approach to its removal was also controversial. A wedge resection or an ultrasound-guided oophorocystectomy was considered. While a large wedge resection may increase the likelihood of securing the microscopic teratoma, it will certainly be a blind approach and may likewise lead to destruction and removal of a large piece of normal ovarian tissue in the process. The ultrasound-guided approach, on the other hand, may be technically difficult and will require hands of an expert. As for this case, the team aimed to do the fastest procedure as possible due to patient's autonomic instability.

CONCLUSION

The link between ovarian teratomas and anti-NMDAr encephalitis is noteworthy. Although not fully fathomed, this connection also imparts evidence that the ovaries play a complex role in a woman's overall health. Future investigations on ovarian teratomas may offer clues to the myriad of autoimmune diseases that are unrecognized and often inappropriately treated. This case demonstrated the need for an increased awareness among gynecologists as we play an important role in the management. The recognition of this underreported disorder must prompt us to look for an ovarian focus because urgent removal of this tumor will reduce the chance of permanent neurologic injury. On the other hand, majority of ovarian teratoma will not trigger or induce this kind of encephalitis but we must be aware that it may still stimulate this form of encephalitis. Management options for confirmed cases must be discussed fully with the family as management may vary on a case by case basis. ■

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