

Case Report

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Giant immature teratoma in a 15 year old causing anti-n-methyl-d-aspartate (anti-nmda) receptor encephalitis-like and Guillain-Barré Syndrome as paraneoplastic manifestations: A case report

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Abstract:

Germ cell tumor is the most prevalent ovarian tumor in young women between 10 and 30 years of age.^[1] However, immature teratomas account for only 20% of the malignant ovarian tumors found in the adolescent age group.^[2] More uncommon is the occurrence of immature teratoma causing anti-N-methyl-D-aspartate receptor (Anti-NMDAR) encephalitis and Guillain-Barré Syndrome (GBS). This is a case of a 15-year-old female, nulligravid, who initially presented sudden behavioral change and symmetrical weakness of both lower and upper extremities with concomitant seizure episodes and with palpable lower abdominal mass. The patient was diagnosed to have GBS and treated with intravenous immunoglobulin causing resolution of neurologic symptoms months after. During the management of GBS, the patient noted increasing abdominal girth. Tumor markers showed elevated alpha-fetoprotein, CA125, and lactate dehydrogenase. An imaging study revealed predominantly solid ovarian mass hence malignancy was considered. Once the medical condition stabilized, the patient underwent fertility-sparing surgery with the final histopathologic result of immature teratoma. The aim of this report is to present a case of anti-NMDAR encephalitis and GBS as paraneoplastic manifestation of immature teratoma.

Keywords:

Encephalitis, Guillain-Barré syndrome, ovarian teratoma, paraneoplastic syndrome

Introduction

Ovarian germ cell tumors (OGCTs) are obtained from primordial germ cells of the ovary that may either be malignant or benign.^[3] It can be broadly divided into those that evolve to imitate the embryonic tissues, such as ectoderm, mesoderm, or endoderm and extraembryonic tissues, such as yolk sac and trophoblasts. The most common malignant germ cell tumors are dysgerminoma, approximately 45%,

then immature teratomas, which account for 20%–25%, and finally, endodermal sinus tumors which are about 10%.^[4] OGCTs are most frequently seen in young women between 10 and 30 years old and represent 70% of ovarian neoplasms in this age bracket.^[5] Approximately one-third of these tumors found in patients younger than 21 years old are cancerous.^[4] Germ cell tumors are most often unilateral, excluding teratomas and dysgerminomas that have 10% and 15% of bilaterality, respectively.

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Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is neoplastic and autoimmune encephalitis with prominent neuropsychiatric symptomatology. The N-methyl-D-aspartate receptor is located in the forebrain and hippocampal region which are responsible in learning and memory.^[6] The NR1 subunit of NMDAR is targeted by immunoglobulin G antibodies triggered by the tumor resulting in internalization of NMDAR and further decrease of synaptic functions, thereby causing neurological symptoms.^[7] Hence, some patients are initially misdiagnosed to have primary psychiatric disorder.

Guillain-Barré syndrome (GBS) is an autoimmune disorder that is thought to have an antecedent gastrointestinal or respiratory infection that cross-reacts with peripheral nerve components, which leads to polyneuropathy, affecting mainly motor, sensory, and occasionally autonomic nerves.^[8] It is the most frequent cause of acute monophasic paralyzing illness among young children.^[9] It has worldwide annual incidence of 0.34–1.34 cases per 100,000 among patients younger than 18 years old.^[10] While all age groups are affected, the incidence is lower in children than in adults; and males are more affected than females by $\times 1.5$. The objective of this paper is to present a case of a Giant immature teratoma in a 15 year old female causing Anti-NMDAR encephalitis and GBS as paraneoplastic manifestations. It aims to discuss the diagnostic laboratories, surgical management, and postoperative plans for the patient.

Case Report

This is a case of a 15-year-old, nulligravid, who consulted a private physician due to abdominal enlargement. Past and family medical histories, personal, menstrual, and gynecologic histories are noncontributory. Developmental history is at par for her age.

History revealed that 5 months before admission, the patient complains of intermittent hypogastric pain with associated palpable abdominal mass. Consult was done, and transrectal ultrasound revealed an ovarian new growth probably malignant. The patient was lost to follow-up due to the coronavirus pandemic.

Four months before admission, the patient exhibited anxiety, agitation, bizarre behavior, and decreased verbal output with associated tingling sensation and paresthesia on toes and fingertips. The paresthesia progressed to symmetrical weakness and difficult mobility of the lower extremities, which later involved the trunk and upper extremities. The patient's medical condition worsened, leading to endotracheal intubation. Diagnostic tests were done, such as blood culture and sensitivity, cerebrospinal fluid (CSF) analysis, cranial computerized

tomography (CT) scan, and cranial magnetic resonance imaging (MRI), which all yielded normal results. The patient had seizure episodes described as twitching of the face with upward rolling of eyeballs with the associated tonic-clonic movement of the upper extremities. The diagnosis then was GBS, hypoxic-ischemic encephalopathy, and healthcare-associated pneumonia. The patient was given intravenous immunoglobulin, antibiotics, and anti-convulsant. Improvement was noted and was discharged eventually after 1 month of hospitalization.

Three months before admission, the patient complained of abdominal enlargement, abdominal tenderness, and difficulty of urinating. The whole abdominal CT scan was done and showed a well-defined complex mass measuring 89.83 mm $\times$ 179.49 mm $\times$ 200.68 mm (AP $\times$ W $\times$ CC) in the abdominopelvic region, probably ovarian in origin. The mass was predominantly cystic, with a multilobulated, heterogeneously enhancing soft-tissue density measuring 90.0 mm $\times$ 61.16 mm $\times$ 60.27 mm along its inferior aspect, exhibiting calcifications and fat components. Tumor markers were elevated, such as CA125 (345.20 U/mL, NV: 0–35 U/mL), alpha-fetoprotein (AFP) (347.84, NV: 0.89–8.78 ng/mL), and lactate dehydrogenase (LDH) (386 U/L, NV: 125–220 U/L). Transrectal ultrasound was also done, showing pelvoabdominal mass suggestive of an ovarian new growth where in laterality is undetermined with malignant features by the International Ovarian Tumor Analysis simple rules and the ADNEX model. Surgical management was advised, but the patient's mother refused by that time. The patient was discharged after the completion of antibiotics.

One month before consult, the patient noted further enlargement of abdominal girth (105 cm) with intermittent abdominal and lower back pain, early satiety, weight loss, and bloatedness. Persistence of the said symptoms prompted consult to attending physician hence scheduled for surgical management.

On admission, the patient was ambulatory and coherent, with normal vital signs and systemic physical examination. There was no cervical lymphadenopathy. The abdomen was distended, with visible veins, and has everted umbilicus with the positive fluid wave. The patient underwent Exploratory laparotomy with right salpingo-oophorectomy with excision of peritoneal implants with bilateral lymph node sampling and with infracolic omentectomy under general anesthesia. On laparotomy, there was approximately 500cc of serous ascitic fluid with no adhesions noted. The right ovary was converted into a pinkish-tan, complex mass measuring 30.0 cm $\times$ 26.0 cm $\times$ 10.0 cm, with a smooth outer surface [Appendix 1a]. Cut sections showed serous

fluid with solid areas of reddish tan, solid, friable mass measuring 26.0 cm in widest diameter with areas of the necrosis and hemorrhage [Appendix 1b and c]. Some solid areas also contained hair and sebum. The right fallopian tube was thinned and stretched out, measuring 15.0 cm in length and 0.5 cm in cross-sectional diameter, with reddish-tan, smooth external surface. There were cream-tan to yellowish tumor implants at the posterior cul de sac measuring 1.0 cm × 1.5 cm in widest diameter, bladder peritoneum measuring 3.0 cm in widest diameter, and peritoneum covering the pelvic sidewalls. The left adnexa, uterus, abdominal organs, and appendix appeared grossly normal. Samples from the omentum and right and left lymph nodes were also obtained. Histopathologic evaluation revealed mature and immature tissues obtained from the embryonic germ layers: ectoderm [Appendix 2a-c], mesoderm [Appendix 2d-f], and endoderm [Appendix 2g-h]. There was also multiple foci of immature epithelium occupying more than 1 but <3 low-power magnification fields confirming it to be an immature teratoma, Grade 2, right ovary [Appendix 3a]. The rest of the specimen is negative for malignancy.

The patient was discharged on the 3rd postoperation with stable vital signs and with improved condition.

Case Discussion

Paraneoplastic neurologic syndrome is a rare neurological disorder caused by abnormal immune system reaction that develops from the remote effects of tumor cells.^[10] They are a diverse group of disorders caused by immune cross-reactivity between the malignant cells and the nervous system. The immunologic response is produced by onconeural antibodies that are directed against the antigens exclusively expressed by the brain.^[11] It is mostly observed in patients with cancers of the lung, gastrointestinal tract, lymphoma, breast, and ovary.^[12] Anti-NMDAR encephalitis is an autoimmune disorder with extensive spectrum of neuropsychiatric symptoms. This somewhat unusual disorder has a typical sequential presentation: first is the acute onset of prodromal symptoms, followed by a psychiatric manifestation, then decrease level of consciousness with focal and clonic seizures, and finally, autonomic disability.^[13] All of the abovementioned symptoms are present in this patient; hence, the clinical manifestation of anti-NMDAR encephalitis was strongly suspected. However, detection of NMDAR antibodies in CSF and/or in the serum still remains the gold standard in diagnosing the disease. The previous studies concluded that the syndrome was a paraneoplastic process because of the antibodies that are generated from the neural elements found within the teratoma. These newly formed onconeural antibodies react with the NR1

subunit of the NMDAR resulting in the characteristic neuropsychiatric syndrome.^[14]

It was reported that anti-NMDAR encephalitis is ×4 more a frequent cause of encephalitis in women under 30 years as compared to other viral encephalitis, such as the herpes simplex virus 1, West Nile virus, and Varicella-Zoster virus.^[14] The establishment of diagnosis is made by detecting anti-NMDA in the CSF. The major immunosuppressive therapies used are high-dose steroids and IVIG or plasma exchanges as the first-line therapy, and the use of rituximab and cyclophosphamide as the second-line therapy. Documented good prognostic factors are the presence of a tumor, immediate treatment, and no admission to an intensive care unit. However, due to the low incidence of the disease, the diagnosis is often delayed and managed as primary psychiatric disorders, with infective encephalitis being ruled out first.^[15]

The patient presented with a prominent psychiatric manifestation, such as anxiety, agitation, memory deficits, and decreased verbal output. It then progressed to a spectrum of neurologic symptoms, from paresthesia of the toes and fingertips to symmetrical weakness of lower and upper extremities with depressed deep tendon reflexes, then to severe pulmonary compromise with concomitant respiratory infection and seizure, with accompanying right adnexal mass. GBS was considered due to the classic progressive ascending motor weakness and eventual areflexia. This is due to molecular mimicry, wherein immune antibodies cross-react with peripheral nerve components. This response is directed toward Schwann cells surface membrane or myelin, resulting to acute polyneuropathy.^[8] Differential diagnoses, such as viral encephalitis, neuroleptic malignant syndrome, cerebrovascular diseases, leptomeningeal metastasis, and drug abuse that may also bring about the patients' symptoms were ruled out based on paraclinical assessment, such as serum and CSF studies, electroencephalography, and MRI imaging, which were all unremarkable. Improvement was noted after giving intravenous immunoglobulin, antibiotics, and anticonvulsant. However, screening for well-characterized paraneoplastic antibodies against intracellular antigens must be done to further support the diagnosis of anti-NMDAR encephalitis and GBS.

Among women of reproductive age, ovarian teratomas are one of the most frequent benign ovarian tumors. Ovarian teratomas, both the mature and immature types, have been linked with anti-NMDAR encephalitis. It has neural components consisting of NR1 and NR2 subunits of the NMDAR, serving as antigenic material. Antibodies of these subunits are generated and circulated in the serum or CSF and bind to the NMDAR found in the hippocampal and forebrain neurons.^[16] It is suspected

that the anti-NMDAR antibody either causes failure of the immune system by ectopic production of NR1/NR2 subunits or a prodromal viral-like illness causes increase in the permeability of the blood–brain barrier to the said antibodies. The NMDAR-to-antibody interaction is thought to be antagonistic and leads to decrease in gamma-aminobutyric acid release. This has been the proposed reason for symptoms, such as psychiatric behavioral changes, autonomic dysregulation, and orofacial dyskinesia.^[16]

Immature teratomas, also known as malignant teratoma, teratoblastoma, or embryonal teratoma, account for only 20% of the malignant ovarian tumors found in the first two decades of life. They comprise <1% of all ovarian malignancies and are uncommon in women after menopause. They consist of immature embryonic structures that can be admixed with mature elements. The diagnosis of this tumor requires the presence of immature elements derived from any of the three germ layers.^[4] In our patient, microscopic sections of the right ovary showed endodermal derivatives, which are skin, adnexal structures, gila, and choroid plexus; mesodermal derivatives which are cartilages (mature and immature), bone, and fat; endodermal derivatives, which are intestinal epithelium, bronchial epithelium, and semi mucinous glands; and finally, multiple foci of immature neuroepithelium occupying more than 1 but <3 low power fields.

Approximately, one-third of the immature teratomas express tumor markers, such as beta-human chorionic gonadotropin (hCG) or AFP. Patients typically present with abdominal distention from the mass and ascites, abdominal tenderness from possible torsion, precocious puberty, and abnormal uterine bleeding probably from hCG production.^[17] Our patient presented with increased abdominal girth, intermittent pelvic pain, urinary symptoms, anorexia, early satiety, and bloatedness. She also had elevated levels of CA125, LDH, AFP, and normal levels of bHCG and HE4.

The International Federation of Gynecology and Obstetrics stage and tumor grade which is dependent on the degree of the immaturity of the various tissues are the basis of prognosis for patients with immature teratoma. Current treatment methods result in cure rates of almost 100% for Stage I malignant germ cell tumors and more than 75% for Stages III and IV patients.^[4] Since our patient is young and has a unilateral tumor, fertility-sparing surgery consisting of unilateral salpingo-oophorectomy with preservation of the contralateral ovary and the uterus with comprehensive surgical staging was done. Immature teratomas have only 2%–5% incidences of bilaterality. Therefore, the normal contralateral ovary was not biopsied because it could lead to future

infertility problems such as ovarian failure or peritoneal adhesions.^[4]

In general, postoperative chemotherapy has been recommended for patients with malignant OGCTs. Significant exceptions include pure dysgerminoma – Stage IA and immature teratoma – Stage IA Grade 1 because surgery alone already provides a high cure rate.^[4] Our patient, after surgery, underwent four cycles of Bleomycin, etoposide, and cisplatin (BEP) regimen every 28 days, which still remains as the standard of therapy.

For patients who have undergone comprehensive surgery plus chemotherapy, it is recommended that serum tumor marker monitoring be done every 3 months for 2 years, and then every 6 months thereafter until 5 years from diagnosis. Patients treated with fertility-sparing surgery should be closely followed with imaging modalities such as pelvic ultrasound or CT evaluations. Follow-up check-up with a thorough physical examination is recommended every 3 months for the first 2 years and less frequently thereafter.^[4]

Summary

If the etiological diagnosis is uncertain in patients presenting with severe psychotic or neurological symptoms, it should be considered that this clinical case can be correlated with Paraneoplastic Syndrome (PNS). Good history taking, thorough physical examination, and a high index of suspicion are imperative to be able to elicit possible differential diagnoses in this case. It should be noted that prompt detection of PNS is important for the early resection of tumor and early initiation of rehabilitation. In addition, OGCTs occur predominantly in children and young women wherein fertility-sparing surgery, such as unilateral salpingo-oophorectomy with preservation of the uterus and the contralateral ovary, may be performed. In general, postoperative chemotherapy with BEP regimen is recommended. Finally, standard surveillance and regular follow-up are advised.

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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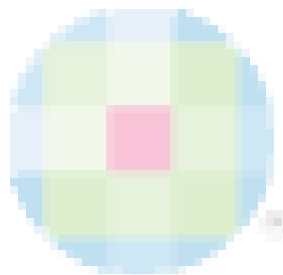
Nil.

Conflicts of interest

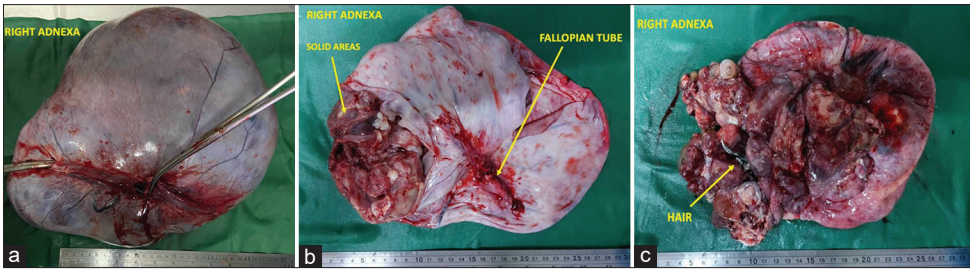
There are no conflicts of interest.

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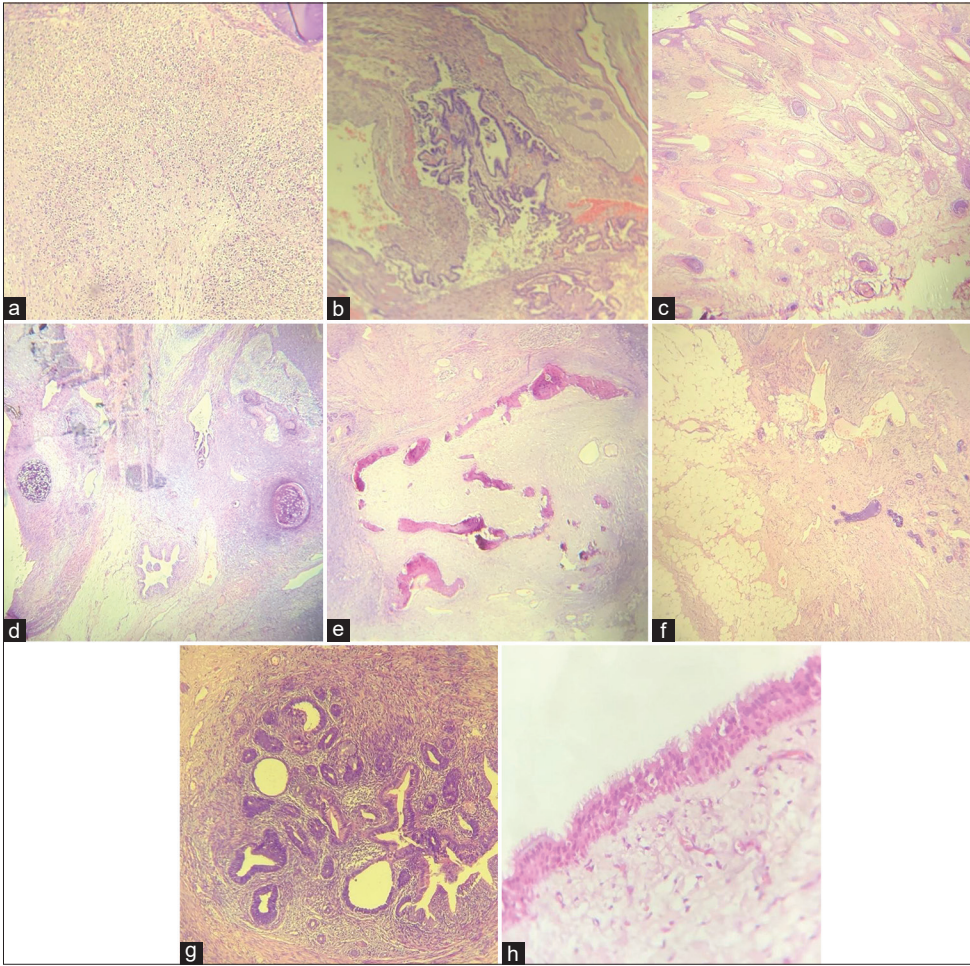
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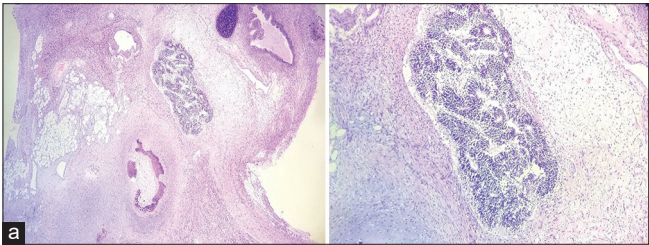
Toreja and Magno: Giant immature teratoma



Appendix 1: (a) The right ovary was converted into a pinkish-tan, complex mass measuring 30.0 cm × 26.0 cm × 10.0 cm. (b) The right fallopian tube was thinned and stretched out, measuring 15.0 cm in length and 0.5 cm in cross-sectional diameter, with reddish-tan smooth external surface. (c) Cut sections showed serous fluid with solid areas of reddish tan, solid, friable mass measuring 26.0 cm in widest diameter with areas of necrosis and hemorrhage. Some solid areas also contained hair and sebum



Appendix 2: (a) Ectodermal derivative: glial cells. (b) Ectodermal derivative: choroid plexus (c) Ectodermal derivative: hair follicle. (d) Mesodermal derivative: immature and mature cartilage. (e) Mesodermal derivative: bone. (f) Mesodermal and endodermal derivative: fat and seromucinous glands. (g) endodermal derivative: Intestinal epithelium. (h) Endodermal derivative: Bronchial epithelium



Appendix 3: (a) Immature neuroepithelium