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Case Report

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Ovarian Teratoma and N-Methyl-D-Aspartate Receptor Autoimmune Encephalitis: Insights Into Imaging Diagnosis of Teratoma and Timing of Surgery

Monica Thiyagarajan[a], Ajit Sebastian[a, c], Dhanya Susan Thomas[a], Anitha Thomas[a], Abraham Peedicayil[a], Vivek Mathew[b]

Abstract

Mature ovarian teratoma is the most common type of germ cell tumor and mostly detected incidentally in women in second or third decade. Recent researches have provided strong evidence between mature ovarian teratoma and encephalitis, which is caused due to the presence of anti-N-methyl-D-aspartate (NMDA) antibodies. We would like to report four patients who had typical neuropsychiatric manifestations, such as abnormal behavior, speech disorder, seizures, movement disorders, loss of consciousness, and autonomic dysfunction. All the patients had prolonged course of disease before the diagnosis of NMDA encephalitis had been made. The importance of timely evaluation of symptomatic young women with serum and cerebrospinal fluid (CSF) NMDA receptor (NMDAR) antibodies is emphasized. Imaging ranging from transvaginal ultrasound to positron emission tomography-computed tomography (PET-CT) will help in arriving at a probable diagnosis. Surgical treatment is the cornerstone of management, and patients responded well post surgery with almost full recovery, with addition of immunotherapy, physiotherapy, rehabilitation providing a vital role. There is significant variation in clinical presentation of encephalitis and thus in time to diagnosis for those with non-specific symptoms, particularly psychiatric ones. The index of suspicion of anti-NMDA encephalitis should be high in young females and involvement of a gynecology team needs to be done. Surgical removal of the teratoma is the key and the gynecology team should not be deterred by the acute symptoms and debilitating nature of the symptoms

Keywords: Mature ovarian teratoma; NMDA; Autoimmune encephalitis; Ovarian teratoma symptoms

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[a]Department of Gynaecologic Oncology, Christian Medical College, Vellore, Tamil Nadu, India
[b]Department of Neurosciences, Christian Medical College, Vellore, Tamil Nadu, India
[c]Corresponding Author: Ajit Sebastian, Department of Gynaecologic Oncology, Christian Medical College, Vellore, Tamil Nadu 632004, India.
Email: sebastian.ajit@gmail.com

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Introduction

The lifetime risk of a woman being operated for ovarian tumor is 5-10%. Mature teratoma is the most common type of ovarian germ cell tumor presenting commonly in the second or third decade of life accounting for 70% of the ovarian tumors. Patients often present with incidental diagnosis of pelvic mass on imaging, which is routinely managed by surgery. In recent years ovarian teratoma has been strongly associated with a type of autoimmune encephalitis associated with anti-N-methyl-D-aspartate (NMDA) antibodies, which had been first described in the year 2007 [1]. Since then, there have been several reports providing evidence towards the strong causal link between ovarian teratoma and anti-NMDA-mediated encephalitis. Surgical removal of the tumor has been described to be associated with significant improvement of the neurological condition. We hereby share our experience with four cases while reviewing literature. While this is now a well described clinical entity, we would like to bring this to the notice of gynecologists, with particular emphasis on problems with imaging diagnosis and timing of surgery.

Case Reports

Case 1

A 38-year-old married female presented to emergency department 19 days after onset of initial symptoms. She had initial history of exaggerated grief response to death of a pet followed by gradual development of altered talk, altered behavior, paranoid thoughts, and delusion of persecution. She had started treatment at a psychiatric facility following which she had developed several episodes of generalized tonic clonic seizures after 13 days of onset of symptoms. After about 16 days since onset of symptoms and anti-epileptics she developed lip smacking, eye rolling, teeth clenching, and abnormal movements of hands. At admission on the 19th day after the onset of initial symptoms her Glasgow Coma Scale (GCS) was E4M5V2, and she had tachycardia, high spiking fevers, orolingual dyskinesia, choreoathetoid movements of eyes along with abnormal movements of eyes. A provisional diagnosis

of autoimmune encephalitis than infective encephalitis was made. She was aphasic with normal power and tone in all four limbs. Electroencephalogram (EEG) showed bihemispheric slow wave discharges. Workup for viral, cryptococal, tubercular, vasculitic etiology was negative. Autoimmune encephalitis panel workup revealed presence of antibodies to NMDA receptor (NMDAR). A positron emission tomography-computed tomography (PET-CT) done revealed a 22 × 21 mm fat density lesion in the right ovary, 7 × 8 mm lesion in left ovary with calcification, and both were non-fluorodeoxyglucose (FDG)-avid suggestive of bilateral ovarian teratomas. Tumor markers were normal. A diagnosis of NMDAR-positive autoimmune encephalitis was made. She was on ventilator support post tracheostomy for respiration, anti-epileptics for seizure control, intravenous immunoglobulin (IVIG) and immunomodulation with rituximab. She underwent laparotomy and bilateral salpingo-oophorectomy 22 days after the diagnosis was made. Intraoperatively there was presence of a 3-cm cyst in right ovary and a 1-cm cyst in left ovary. Histopathology was reported to be bilateral mature ovarian teratoma. She developed postoperative complication of burst abdomen on postoperative day (POD) 5, for which she underwent re-laparotomy and resuturing. Patient improved symptomatically, steroids were discontinued and four doses of rituximab were completed. At discharge her GCS was E4M6VT, communicating well through writing and on nasogastric (NG) feeds. She was discharged on three oral anti-epileptics. When she came for review after 3 months of surgery she was seizure free, with no involuntary movements. Tracheostomy decannulation was done 6 months post procedure after adequate swallowing was present and no evidence of aspiration was present on assessment. At the end of 21 months antibody to NMDAR was negative. At 32-month follow-up the patient was in remission, clinically better, and was on the sixth monthly dose of rituximab after completion of five cycles.

Case 2

A 17-year-old unmarried girl presented with fever, auditory, visual hallucinations, altered sensorium, stereotypical oromandibular movements, repetitive seizures and severe limb dyskinesia. She had already been diagnosed to have autoimmune encephalitis with NMDAR antibodies elsewhere. Over the preceding 5 weeks, she had been treated with steroids and IVIG. Ultrasound abdomen had shown only a non-specific bright signal in the region of the right ovary, while CT and magnetic resonance imaging (MRI) abdomen were unremarkable. She was on tracheostomy and had wounds from restraints used for the severe limb dyskinesia. She did not have any meaningful eye opening. Motor GCS could not be calculated as she had continuous high amplitude involuntary movements (the limb dyskinesia). Clinical examination revealed that bilateral pupils were equally reactive to light, presence of stereotypical movements of limbs, normal power, tone, bulk of muscles, normal deep tendon reflexes, no cerebellar signs. Tumor markers were normal. MRI brain was suggestive of diffuse cerebral edema.

On the fifth day of admission (sixth week since onset of symptoms), she underwent laparoscopic examination of the right ovary followed by right salpingo-oophorectomy. She had a bulky right ovary which on cut section showed small dermoid cyst with normal left ovary. Biopsy was suggestive that the lesion was less than 1 cm ranging from 0.3 to 0.6 cm. Histopathology was reported as a mature cystic teratoma. She also had four cycles of plasmapheresis, four cycles of bortezomib. During her extended 6-month hospital stay she had complications of ventilator-associated pneumonia, sepsis, diabetes insipidus, and hypothermia, which were managed accordingly. She improved with treatment, but regained only minimal consciousness, inconsistent obeying of commands. Facial and limb dyskinesia was reduced and she was on steroids and four anti-epileptics at discharge. She underwent rehabilitation in the form of physiotherapy, occupational therapy, swallowing therapy, and chest physiotherapy. On follow-up after 1 year she was more consistent with recognition and communication, had significant improvement of dyskinesia with residual orofacial dyskinesia and dystonic posturing present, but was still on NG tube feeds and tracheostomy could still not be decannulated.

Case 3

A 26-year-old female presented with high-grade fever, headache followed by complaints of altered sensorium, irrelevant abusive talk, abnormal oral movements, and recurrent seizures for 1 month. She had been on respiratory support with ventilator since 7 days of onset of symptoms. She was treated with IVIG at a local hospital and referred for further management. She presented with GCS of E4M5VT, facial grimacing, perioral dyskinesia, stereotypical movements of bilateral upper limbs. Workup for viral, vasculitic, infective etiology was negative. Autoimmune encephalitis panel revealed antibodies to NMDAR. EEG showed bihemispheric slow waves. MRI brain was unremarkable. Ultrasound abdomen was suggestive of cystic lesion in both ovaries. Tumor markers were normal. She underwent laparotomy, right salpingo-oophorectomy and left cystectomy. Intraoperatively there was a right-side 4 × 3 cm cyst which on cut section revealed sebaceous material; and left side 3 × 2 cm. Biopsy of the surgical specimen was reported to be bilateral mature cystic teratoma. She was treated with IV methylprednisolone and four doses of rituximab. Seizures were under control on four anti-epileptics. She was rehabilitated with physiotherapy, occupational therapy, and speech therapy. Patient is alive and doing well with NMDAR negative at the end of 19 months.

Case 4

A 28-year-old female presented to neurology outpatient with history of headache 6 months ago, multiple episodes of vomiting, tremors, followed by altered sensorium, and difficulty walking with jerky movements of limbs. She had been bedridden for the past 5 months. After initial evaluation at hometown in view of suspicion of postinfectious cerebellitis she was treated with steroids and acyclovir. Since there was worsening

Table 1. Summary of Cases

	Case 1	Case 2	Case 3	Case 4
Age	38	17	26	28
Parity	2	Nulliparous	2	2
Time since symptoms to referral	26 days	43 days	38 days	180 days
Fever	+	+	+	-
Abnormal psychiatric symptoms behavior	+	+	+	+
Speech disorder	+	+	+	+
Seizure	+	+	+	-
Movement disorder	+	+	+	+
Loss of consciousness	-	-	-	-
Autonomic dysfunction	+	+	+	-
Modified Rankin score	5	5	5	4
CSF analysis				
Count	6/mm^3	3/mm^3	14/mm^3	1/mm^3
Glucose	73 mg/dL	55 mg/dL	82 mg/dL	66 mg/dL
Protein	36 mg/dL	21 mg/dL	25 mg/dL	61 mg/dL
CSF PCR for viruses	Negative	Negative	Negative	Negative
CSF culture	Sterile	Sterile	Sterile	Sterile
NMDAR antibodies in CSF	2+	2+	2+	Negative
NMDAR antibodies in blood	Not done	2+	Not done	Negative
EEG	Bihemispheric slow wave	Bihemispheric slow waves	Bihemispheric slow wave	Not done
MRI brain	Normal	Diffuse cerebral edema	Diffuse cerebral edema	Normal
Medical treatment	Methylprednisolone, IVIG, rituximab	IVIG initially, methylprednisolone throughout, later plasmapheresis, rituximab, bortezomib	Methylprednisolone, rituximab	Plasmapheresis, methylprednisolone, rituximab
Need for tracheostomy	Day 40 of symptoms	Day 10 of onset of symptoms	7 days after symptom onset	No
Period of hospital stay	53 days	180 days	36 days	28 days
Neurological outcome				
Follow-up time	32 months	25 months	19 months	4 months
NMDAR	Negative	2+	Negative	
Modified Rankin score	0	5	0	1
Imaging modality	PET-CT	USG, CT, MRI	USG	PET-CT
CA-125	Not done	10.40	15.8	8.92
b-hCG	1.4	< 0.100	< 0.100	< 0.100
CEA	Not done	0.67	3.01	Not done
AFP	2.77	Not done	1.9	1.4
LDH	798	Not done	503	358
Type of surgery	Laparotomy BSO	Laparoscopic RSO	Laparotomy RSO, left cystectomy	Laparoscopic RSO
Anesthesia	General anesthesia	General anesthesia	General anesthesia	General anesthesia

Table 1. Summary of Cases - *(continued)*

	Case 1	Case 2	Case 3	Case 4
Timing of surgery from date of admission	22 days	5 days	4 days	21 days
HPE report	B/L mature ovarian teratoma	Mature cystic teratoma: right ovary	B/L mature cystic teratoma	Mature cystic teratoma
Bilaterality	+	-	+	-
Size of the tumor	Right cyst: 3 × 3 × 2cm, left cyst: 4 × 3 × 2 cm	Ovary: 2.6 × 1.5 × 1 cm; 3 cystic spaces 0.3 - 0.6 cm with hair	Right: 2 × 1 cm, left: 2 × 1.5 × 0.7 cm	Cyst: 5 × 3 cm

CSF: cerebrospinal fluid; NMDAR: N-methyl-D-aspartate receptor; PCR: polymerase chain reaction; EEG: electroencephalogram; MRI: magnetic resonance imaging; CA125: cancer antigen 125; AFP: alpha fetoprotein; hCG: human chorionic gonadotropin; LDH: lactate dehydrogenase; CEA: carcinoembryonic antigen;

of symptoms she came to our institution for further management. On clinical examination there was slurred speech with echolalia, bilateral opsoclonus, generalized tremors with stimulus sensitive action myoclonus; bradykinesia, dystonia with rigidity. She had grade 4 power in all four limbs. She had dysdiadokinesia, titubation, and ataxic gait. MRI brain showed no intracranial abnormality. Workup for anti-Sjogren's syndrome-related antigen A (SSA), anti-SSB, double stranded DNA (dsDNA), anti-nuclear antibody (ANA), anti-thyroglobulin, thyroid peroxidase was negative, and viral polymerase chain reaction (PCR) was also negative. Blood and serum autoimmune encephalitis panel were negative. Wilson's disease and vasculitis workup were negative. PET-CT revealed a right ovarian tumor with normal tumor markers. A diagnosis of seronegative autoimmune encephalitis was made. She was initiated on therapeutic plasma exchange and started on methylprednisolone. She underwent laparoscopic right salpingo-oophorectomy with intraoperative findings of right ovarian cyst of 6 × 6 cm. The histopathology of the specimen was reported to be mature cystic teratoma. She also had a history of left salpingo-oophorectomy in view of benign cyst 5 years back, for which biopsy report was not available. She was also initiated on rituximab. Patient showed improvement postoperatively in the form of improved sensorium, decrease in opsoclonus and truncal stability. Patient was symptomatically better when she came for review at 4 months on antiepileptics, rituximab and steroids. A summary of all the cases is given in Table 1.

Discussion

Mature ovarian teratomas are the most common ovarian germ cell tumors which are mostly benign with up to 1.2% risk of malignant transformation. They constitute 70% of the ovarian germ cell tumors, presenting commonly in the second decade. In most of the cases of mature ovarian teratoma the diagnosis is incidental with the patient being asymptomatic, with few patients presenting with abdomen pain due to underlying torsion or rupture leading to surgical emergencies. Few rare presentations are growing teratoma syndrome, NMDAR encephalitis, and autoimmune hemolytic anemia. Anti-NMDA encephalitis is a type of autoimmune encephalitis most commonly but not always associated with ovarian teratomas. The presence of underlying ovarian neoplasm in such patients varies from 26.9% to 38% [1].

NMDARs are ion channels that are gated by glutamate which is an excitatory neurotransmitter, present throughout the central nervous system (CNS). They play a significant role in learning, memory and synaptic plasticity. NMDARs are composed of variable sub-units. They are generally tetramers consisting of two GluN1 subunits plus either two GluN2 or GluN3 subunits. In anti-NMDA encephalitis the antibodies are generally directed against the N1 subunit which will eventually decrease the expression of NMDARs, thus causing the neurological and psychiatric symptoms [2]. The development of antibodies had been reported to be due to the expression of the ectopic NMDAR receptors by the neural elements of the mature teratoma which could stimulate the antibody production.

When the disorder was first described the striking features associated were that young females were affected with psychiatric symptoms, seizures, cognitive disturbances and had CSF analysis suggestive of antibodies against antigens present in the hippocampus; with underlying ovarian teratoma [3]. Over the years this specific type of encephalitis has been studied and reported with several case series and case reports. The common age of presentation is around 20 years [4], and almost 90% affects females. In our group of patients there is similar presentation in the second or third decade.

The symptom complex has been well described and diagnostic criteria have been put forth which comprise of clinical features such as abnormal behavior, speech dysfunction, seizures, movement disorders, decreased level of consciousness, autonomic dysfunction or central hypoventilation [5]. It is to be noted that presence of three of the enlisted symptoms along with teratoma has been considered adequate to make a probable diagnosis of anti-NMDAR encephalitis though the identification of IgG GluN1 antibodies is needed to make a definite diagnosis. Studies have highlighted several patients being admitted to psychiatric facility first and referred to neurology when doubt arises due to treatment failure. Thus, most patients generally develop psychiatric symptoms which are followed by neurological symptoms.

Pleocytosis in CSF is related finding in these conditions.

Other findings include EEG abnormality in the form of focal or diffuse slow wave. MRI of brain is generally normal in more than 50% of the cases. There can be variable presentations on MRI such as abnormality limited to hippocampus alone or present in other areas also. Those with hippocampal lesions were associated with poorer prognosis [6]. Treatment is initiated with steroid, IVIG, plasmapheresis followed by addition of steroid-sparing agent like rituximab. The surgical treatment by removal of the teratoma has been associated with good prognosis even with lesions as small as 1 cm. There is 81% improvement in the neurological outcome following immunotherapy along with surgical removal of the teratoma [3].

Mostly the tumors are unilateral. A recent review suggests that among the available literature only 24 cases had bilateral tumors with few being a combination of mature and immature teratoma [7]. Few reports have suggested the association of anti-NMDA encephalitis with other types of ovarian tumors also, such as immature teratoma, sex cord stromal tumor, and mucinous cystadenoma. Two patients had bilateral tumors which are generally rare, one was managed by bilateral oophorectomy, and the other patient had fertility-sparing procedure with oophorectomy and cystectomy. Both patients had good outcome and are in remission now with no antibodies on follow-up.

It is to be noted that the symptom complex of our patients described were fitting into the diagnostic criteria; with the psychiatric symptoms preceding the neurologic symptoms. The clinical features were strongly pointing towards a diagnosis of anti-NMDA encephalitis for all four cases, and there was no delay in evaluation for NMDAR antibodies; following which imaging confirmed ovarian teratoma. The current trend is to do NMDAR antibody test in both serum and CSF. Though in case 4 the antibodies to NMDAR were not detectable, the presence of three characteristic symptoms associated with mature teratoma led to a probable diagnosis; and we proceeded with surgery. A suspicious ovarian abnormality in a patient with typical clinical presentation should also be investigated even if the NMDA antibody itself is negative.

The radiological diagnosis of ovarian teratoma is dependent on the combination of imaging characteristics of different mature ectodermal tissues within the ovary. Thus all three modalities of ultrasonography (USG), CT and MRI can be complementary for a given patient with autoimmune encephalitis. In view of the high prevalence, and the importance of surgery in refractory cases, there could be an argument for exploratory laparotomy. Even in the absence of a definite radiological diagnosis of ovarian teratoma, looking closely at the ovary with any suspicious abnormality could find a teratoma as in case 2.

It is widely believed that the early surgical removal of the tumor during the acute phase of the disease is a very critical step in management of such patients. Bilateral exploration and removal should be considered in the patients who have severe refractory disease and who have completed family. Fertility-sparing surgery can be considered if the family wishes.

Patients showed good recovery followed by multimodality treatment. The need for rigorous structured rehabilitative measures should be emphasized.

Learning points

There is significant variation in clinical presentation of encephalitis and thus in time to diagnosis for those with non-specific symptoms, particularly psychiatric ones. However, once the diagnosis has been suspected in a young female, a gynecology team needs to be involved right away. Removal of the teratoma becomes even more important for those who are refractory to initial immunotherapy. The acute symptoms should not deter us from offering surgical removal of the tumor. Since there is chance of bilaterality of tumor it is prudent to carefully analyze evidence of tumor both on preoperative imaging and intraoperatively. The presenting age group makes the option of fertility-sparing surgery a necessity even in cases with bilateral tumors which has been stated as a safe option.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

Informed written consents have been obtained from the patients for publication process.

Author Contributions

MT, AS, VM were involved in the compilation and editing of the report. AS, DST, AT, AP, VM were involved in diagnosis and treatment of the patients.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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