

Ovarian teratoma with anti-N-methyl-D-aspartate receptor encephalitis, a type of limbic encephalitis: a review of the literature and a case report in Korea

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Summary

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a type of limbic encephalitis that is resulted by an autoimmune processes; it is a rare autoimmune encephalitis caused by the NMDA receptor antibody secreted by all kinds of tumors. This paraneoplastic syndrome is frequently associated with ovarian teratomas; however, neural cells expressing anti-NMDAR may also be involved in the disease. We report a patient with a case of anti-NMDAR encephalitis associated with an ovarian teratoma, and present a literature review of 16 cases of anti-NMDAR encephalitis in Korean women.

Key words: Anti-N-methyl-D-aspartate receptor encephalitis; Teratoma; Anti-NMDAR autoimmune encephalitis with teratoma; Encephalitis; Ovarian neoplasm.

Introduction

Germ cell tumors constitute approximately 15%-20% of ovarian tumors, and teratomas are the most common germ cell tumors derived from all three embryonic germ layers [1]. This tumor is associated with paraneoplastic syndromes, such as anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. Anti-NMDAR encephalitis is an autoimmune disease, first reported in 2005 [2]. It is a type of limbic encephalitis, characterized by various clinical symptoms including abnormal behavior, dyskinesia, seizures, psychiatric symptoms, and potentially life-threatening central hypoventilation and dysautonomia [3].

There are no previous reports on these tumors in the field of gynecology in Korea, and only a few case reports in the field of neurology. We describe a case of anti-NMDAR encephalitis successfully treated with a laparoscopic teratoma cystectomy.

Case Report

A 36-year-old woman (gravida 1, para 1), who had no history of medical or psychiatric problems, visited our hospital with euphoric behavior that started 5 days previously, and violent behavior that started 1 day previously. Imaging, serology, and cerebrospinal fluid (CSF) examinations as well as a tumor marker assessment were performed. However, there were no specific findings in brain magnetic resonance imaging (MRI), computed tomography (CT), serology, or CSF examinations. Because she abruptly presented

with drowsiness, the initial diagnosis was viral encephalitis. She was admitted to the intensive care unit (ICU) and started on anti-viral treatment (acyclovir 750 mg IV). Sedation was continued because of her persistent violent behavior. The premenopausal-risk of ovarian malignancy algorithm (pre-ROMA) value was 17.5%, and other tumor marker values (CA 125, CEA, AFP) were normal. Additional CSF tests were conducted on the 7th day of hospitalization, but no specific details were obtained. Mild-to-moderate diffuse cerebral dysfunction was observed on the electroencephalography (EEG). Steroid (methylprednisolone 1,000 mg IV) administration was started based on the possibility of autoimmune encephalitis. After 3 days, her oxygen saturation decreased, and the patient was diagnosed with pneumonia. Steroid administration was discontinued and intubation was performed because of aggravated pneumonia.

Based on various test results, there was no other suspected disease besides autoimmune encephalitis, and additional tests were performed. On the 14th day, an abdominal CT was performed because of the high pre-ROMA level, which showed a 2-cm right ovarian teratoma (Figure 1). On the 15th day, our obstetrics and gynecology department received an operative request, but the operation was suspended because of the high risk of surgery. An autoimmune antibody test was performed on the 20th day because the patient remained in a state of confusion. With empirical antibiotic therapy, her lung condition improved allowing for extubation on the 22nd day. However, she experienced a

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Figure 1. — A 2-cm well defined, heterogeneous attenuated oval mass, with a fat component in the right adnexa; a right ovarian teratoma is suspected.

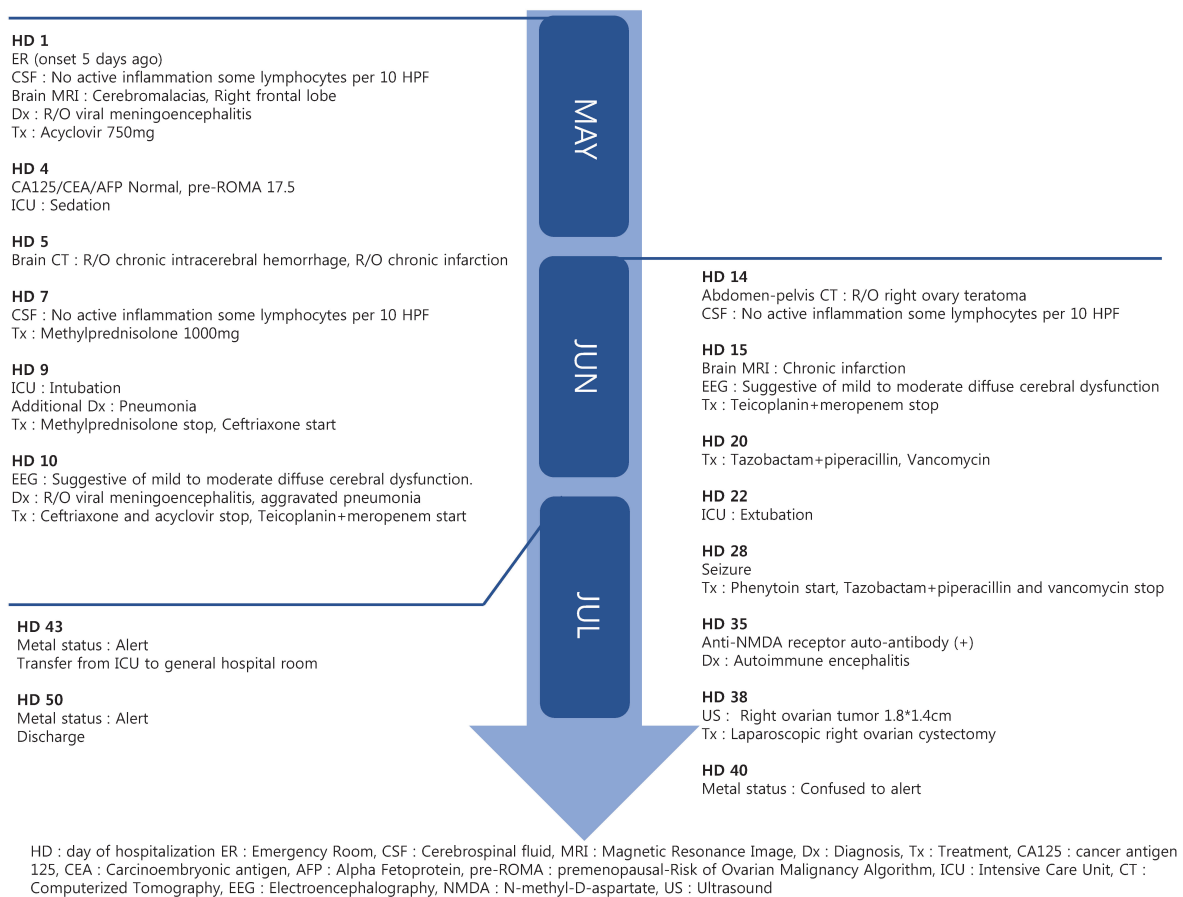


Figure 2. — Timeline of events.

seizure, therefore anti-seizure medication (Phenytoin) was administrated on the 28th day. On the 35th day of hospitalization, an autoimmune synaptic encephalitis antibody test confirmed anti-NMDAR antibody positivity, and thus an ovarian teratoma removal operation was requested once again.

For the NMDAR expressing ovarian teratoma, a laparo-

scopic ovarian cystectomy was performed on the 38th day. Histologically, the ovarian mass was confirmed to be a benign cystic teratoma, partially opened, with a yellowish-brown, greasy material, and hair shafts in the lumen.

After the operation, the patient's general condition and neurological symptoms dramatically improved, and she was discharged on the 50th day of hospitalization. At the

Table 1. — *Clinical features of the 16 women with anti-NMDAR encephalitis in Korea.*

Case No.	Ref.	Age	Prodromal Sx	Neuropsychiatric Sx and nomic Dysfunction	Auto- Medical Hx	Tumor	Time to Dx (days)	HD (days)	ICU Care	Primary Tx	Tx after Dx	Outcome
1	[14]	27	-	Irritable mood, disorganized speech, comatose mentality, catatonia, tremor, rigidity, myoclonic movements of arms, sudden involuntary actions, loss of verbal communication	Grave's Dz	-	4	-	-	General management of steroid-induced psychosis	MP. IVIG. Rituximab. MM	Substantial improvement (1 mo)
2	[15]	9	-	Cognitive disturbance, mutism, irritability, agitation, abnormal phonation, mild bilateral stiffness in upper extremities, auditory and visual hallucinations	-	-	34	107	+	Risperidone, paroxetine, benztropine	MP. IVIG. Rituximab	Substantial improvement (5 mo)
3	[16]	37	Cough, general malaise, poor appetite, insomnia, transient loss of consciousness	Confusion, depression, memory deficit, impaired speech, disorientation	HTN	4.8 cm Lt ovarian teratoma	2	16	-	Olanzapine, quetiapine, lorazepam, IVIG, acyclovir	Tumor resection	Substantial improvement
4	[17]	25	Hyperactivity, mood lability, depression, poor appetite, auditory hallucination	Dyspnea, agitation, aggressive behaviors, decreased consciousness, oro-lingual-facial dyskinesias, hypoventilation	-	6.0 cm teratoma in Lt anterior mediastinum	9	45	+	MP, IVIG, acyclovir, levetiracetam	Tumor resection, rituximab, MM, tocilizumab	No improvement (transfer to another hospital)
5	[18]	6	Fever, seizures, disorientation, vomiting	Lethargic, mutism, dysphagia, seizure (focal seizure involving twitching of the left side of face and jerking of left arm) generalized bizarre and jerking movements, frequent alterations in mental status	-	Rt ovarian teratoma	-	-	-	Vancomycin, cefotaxime, acyclovir, IVIG, phenobarbital, fosphenytoin, levetiracetam	Tumor resection, rituximab, MP	Substantial improvements (6 mo)
6	[19]	70	Confusion, cognitive dysfunction, common cold	Confusion, disorientations, speech impairment, aggressive behaviors, mood swings	HTN	-	10	-	-	MP, antiepileptic drugs	IVIG, rituximab	Substantial improvements (1 yr)

Table 1. — *Continued.*

Case No.	Ref.	Age	Prodromal Sx	Neuropsychiatric Sx and Auto-nomic Dysfunction	Medical Hx	Tumor	Time to Dx (days)	HD (days)	ICU Care	Primary Tx	Tx after Dx	Outcome
7	[20]	44	Dyslexia, phonemic paraphasia, mild cognitive dysfunction	Depression, irritability, visual hallucination, global aphasia, progressive psychosis, bizarre arm movements	-	-	-	-	-	Oral antiplatelet agent, donepezil	MP, IVIG, rituximab	Substantial improvements (1 yr)
8	[21]	36	Abnormal behavior, frequent mood changes, fever, chills. Headache	Frequent mood changes, visual hallucinations, insomnia, hyperactivity, aggressive behaviors, catatonia, impaired speech, hypertension, tachycardia, hyperventilation	-	5.5 cm Rt ad-nexal teratoma	26	46	-	Lorazepam, valproic acid, cefazolin, levofloxacin, ampicillin/sulbactam	MP, tumor resection	Substantial improvements (1 mo)
9	[22]	20	-	Abnormal behavior, mood changes, agitation, depression, confusion, dyskinetic movements, hypoventilation, convulsive activities, muscle rigidity	-	Bilateral ovarian teratomas	54	72	+	Acyclovir, valproic acid, levetiracetam, phenytoin, carbamazepine	Tumor resection	Substantial improvement (4 mo)
10	[23]	31	Fever, chills. Headache	Impaired speech, memory deficit, inappropriate laughing, abnormal behavior, fever, irritability, agitation, dyskinesia, oro-lingual-facial dyskinesias, hypersalivation, tachycardia, hypotension, ileus, choreoathotoid movement	PA 6 wks	9 cm Rt ovarian teratoma	50	167	+	Acyclovir, levetiracetam, dexamethasone, Clonazepam, levodopa, clozapine	Tumor resection	Substantial improvement
11	[24]	28	Mild fever, headache, sleep disturbance	Abnormal behavior, hypoventilation, epileptic seizure, hypoventilation, dyskinesia, comatose mentality	PA 7 + 4 wks	5 cm Rt ovarian teratoma	28	154	+	Acyclovir, levetiracetam	MP, IVIG, tumor resection, Rituximab	Substantial improvement (12 mo)
12	[25]	22	-	Intermittent involuntary movement on the left hand, blepharospasm, irrelevant speech, anxious, irritability, visual hallucination, Catatonia, Left upper extremity abnormal movement, tonic posture (Lt > Rt)	-	-	-	-	-	-	MP	Substantial improvement (11 wks)

Table 1. — *Continued.*

Case No.	Ref.	Age	Prodromal Sx	Neuropsychiatric Sx and Auto-nomic Dysfunction	Medical Hx	Tumor	Time to Dx (days)	HD (days)	ICU Care	Primary Tx	Tx after Dx	Outcome
13	[25]	30	-	Anxiousness, left head deviation, Left hand tonic seizure, irritable, violent behavior, decreased verbal output, visual hallucination Catatonia, rigidity (Left tonic posture), mutism, mild fever, tachycardia	-	-	-	-	-	-	MP electroconvulsive Tx	Substantial improvement (23 wks)
14	[25]	17	-	Anxiety, focal seizure on the Left upper extremity and face, psychotic behavior, visual hallucination, Catatonia, rigidity, tonic posture (Lt > Rt), opisthotonic posture, orofacial-tongue dyskinesia, mutism, mild fever, tachycardia, tachypnea, intermittent hypoventilation	-	-	-	-	-	-	MP, IVIG, electroconvulsive Tx	Limited improvement (2 wks)
15	[26]	31	Visual and auditory hallucinations, dystonia of both arms, catatonia	Oculogyric crisis, oro-lingual and limb dystonia, gait disturbance, tachycardia, hypersalivation, dysphagia, rigidity and dystonia of all extremities, decreased awareness, speech disturbance	-	-	-	-	+	Risperidone, clonazepam, baclofen	MP, IVIG, cyclophosphamide, PE	Limited improvement (1 mo)
16	Present study	36	Abnormal behavior, hyperactivity, violent behavior	Drowsy metal status, agitation, violent behavior, disorientation, eye upper deviation	-	2 cm right ovarian teratoma	34	49	+	Acyclovir, MP	Tumor resection	Substantial improvement (3 mo)

Sx: symptom, Hx: history, HD: hospitalization, HTN: hypertension, Dz: disease, PA: pregnant at, MP: methylprednisolone, IVIG: intravenous immunoglobulin, PE: plasma exchange, OMM: oral mycophenolate mofetil, MM: mycophenolate mofetil.

3-month follow-up, the patient had returned to a normal life and showed normal findings on her EEG. The timeline of events is described in Figure 2.

Discussion

Anti-NMDAR encephalitis associated with teratoma usually develops in young women [4]. The exact incidence of the disease is unknown, but it is more prevalent in the Asian and African populations [5]. Of the reported patients, 80% are women, and 56% of the patients have incidental ovarian teratomas [3, 6, 7]. In order to better understand the clinical features of the patients with anti-NMDAR encephalitis, we reviewed all of the reported cases in Korean women (Table 1). According to the anti-NMDAR encephalitis study in Japan, the median age of patients at the time of symptom onset was 25.8 years (range, 17-33 years), and the duration of hospital stay ranged from 2 to 14 months (mean, 7 months) [8]. In our review, the median age was 28 years (range, 6-70 years), and the duration of hospital stay ranged from 2 to 24 weeks (mean, 12 weeks). In the review of anti-NMDAR encephalitis with mature teratomas in Spain, the mean tumor size was 6.7 ± 5.7 cm (range, 1-22 cm) [9]. In our review, the mean tumor size was 5.38 cm (range, 2-9 cm).

Although the mechanism by which anti-NMDAR encephalitis causes neurological symptoms is unclear, animal studies suggest that anti-NMDAR antibodies cross-link to target receptors and induce NMDAR depletion, resulting in neurological symptoms [10]. In one animal study, the antibody entered the rodent's brain and reduced the neuronal anti-NMDAR surfaces, leading to neurological symptoms [11].

The diagnostic criteria for anti-NMDAR encephalitis are presented below. A diagnosis of probable anti-NMDAR encephalitis is made when all three conditions are present: 1) rapid onset (< 3 months) of at least four of the major groups of symptoms (abnormal behavior or cognitive dysfunction, speech dysfunction, movement disorder, decreased level of consciousness, autonomic dysfunction, or central hyperventilation); 2) at least one of the following laboratory test abnormalities (abnormal EEG findings, CSF with pleocytosis, or oligoclonal bands); and 3) reasonable exclusion of other disorders. Moreover, definite anti-NMDAR encephalitis is diagnosed with the presence of one or more of the major groups of symptoms and the presence of IgG anti-GluN1 antibodies, following reasonable exclusion of other disorders. Antibody testing should include CSF testing. If only serum is available, confirmatory testing should be included (live neurons or tissue immunohistochemistry with a cell-based assay) [12].

Anti-NMDAR encephalitis with teratoma is a rare disease. Gynecologists have difficulty encountering these cases, as the patients visit the hospital because of neurological symptoms. There is still no agreed-upon treatment, but removal of ovarian lesions (if present) and immunotherapy are recommended. The following interventions were

proposed for the immunotherapy treatment: first-line immunotherapy including steroids, intravenous immunoglobulins, and plasmapheresis; and second-line immunotherapy including rituximab and cyclophosphamide [4]. It is also known that early removal can lead to a good prognosis, if an ovarian teratoma is present [4, 13]. In our review, of 16 patients with anti-NMDAR encephalitis, 8 had tumors, and 7 of those had ovarian teratomas. Of the seven patients with ovarian teratomas, two were treated without immunotherapy (Table 1). Additionally, the symptoms dramatically improved after the removal of the teratoma. Therefore, it is important for gynecologists to recognize the disease and perform surgery as soon as possible.

The first Korean case of treating anti-NMDAR encephalitis with teratoma removal was reported in the *Journal of Clinical Neurology* in 2014 [5]. Anti-NMDAR encephalitis usually begins with symptoms such as schizophrenia and flu. In our review, five anti-NMDAR encephalitis cases were initially diagnosed and managed as schizophrenia, and three cases were diagnosed and managed as the flu. Intriguingly, there were two maternal cases, both of which had a miscarriage about a week after hospitalization (Table 1). The mechanism that led to the miscarriage was unclear. Additional research is needed to understand the disease. It is difficult for gynecologists to consider surgery for a patient with a small teratoma who is in the ICU or pregnant. However, if anti-NMDAR autoantibodies are present, it is recommended to perform surgery as soon as possible, irrespective of the clinical state of the patient.

Thus, if anti-NMDAR encephalitis is suspected in a patient with behavioral or neurological changes, an evaluation of anti-NMDAR antibodies and ovarian tumors should be performed.

Ethics Approval and Consent to Participate

We have received IRB approval for this case report (IRB File No: KANGDONG 2019-10-013) and obtained written consent from the patient.

Authors' Contributions

SP, JL designed the research study and performed the research. SY, SJ provided help and advice. SP, JL analyzed the data and wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

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