



Case Report

Anti-NMDAR encephalitis with ovarian teratomas: Review of the literature and two case reports

Hsiao-Chen Chiu^a, Yu-Ching Su^b, Su-Cheng Huang^a, Han-Lin Chiang^b,
Pei-Shen Huang^{c, d, *}

^a Department of Obstetrics and Gynecology, Taipei Tzu-Chi Hospital, The Buddhist Tzu-Chi Medical Foundation, Taipei, Taiwan

^b Department of Neurology, Taipei Tzu-Chi Hospital, The Buddhist Tzu-Chi Medical Foundation, Taipei, Taiwan

^c Department of Obstetrics and Gynecology, Taipei Medical University Hospital, Taipei, Taiwan

^d Department of Obstetrics and Gynecology, College of Medicine, Taipei Medical University, Taipei, Taiwan

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ABSTRACT

Objective: Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a paraneoplastic syndrome associated with ovarian teratomas. Anti-NMDAR encephalitis patients typically present with prominent psychiatric symptoms, seizures, and involuntary movements; further, they rapidly progress to unresponsiveness with central hypoventilation and dysautonomia.

Case report: This paper presents two anti-NMDAR encephalitis cases with ovarian teratomas and reviews 13 anti-NMDAR encephalitis clinical case reports in Taiwan, of which six involved ovarian tumors, five being mature teratomas. Patients presented with acute onset of psychiatric symptoms and subsequently developed coma within a few days. Anti-NMDAR encephalitis usually occurs in young women and is often associated with ovarian tumors, specifically teratomas. Ovarian cystectomy or oophorectomy was performed, which markedly improved cognitive function.

Conclusion: Paraneoplastic neurological conditions associated with ovarian teratomas represent a fascinating disease process. Identifying the gynecological cause of a neurological condition, particularly in young women, followed by prompt treatment can remarkably improve clinical conditions and, thus, be lifesaving.

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Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a paraneoplastic syndrome associated with ovarian teratomas; patients typically present with prominent psychiatric symptoms, seizures, and involuntary movements and rapidly progress to unresponsiveness with central hypoventilation and dysautonomia.

Although the incidence of anti-NMDAR encephalitis associated with ovarian teratomas differs across studies, it is severe and potentially life threatening. This report describes two rare anti-NMDAR encephalitis cases associated with ovarian teratoma and reviews 13 anti-NMDAR encephalitis cases from Taiwan.

Case report

Case 1

The first patient was a 27-year-old female with no history of medical or psychiatric problems who presented with vomiting accompanied by poor appetite, headache, general malaise and intermittent fever (38 °C) for 2 weeks. She was first diagnosed with acute gastritis and prescribed drugs for symptomatic treatment. However, she later developed incoherent speech and an abnormally aggressive behavior, including shouting loudly at her family. She was brought to Taipei Tzu Chi Hospital emergency department, wherein she presented with poor eye contact and unresponsiveness to questioning during an interview. Her Glasgow coma scale score was E4V3M4. Her neurological evaluation was limited by her apathetic and uncooperative state. Her laboratory results revealed only hyponatremia (Na: 120 mmol/L). She was admitted to the nephrology ward for further evaluation and treatment on May 14, 2015.

* Corresponding author. Department of Obstetrics and Gynecology, Taipei Medical University Hospital, No. 252, Wuxing St., Xinyi Dist., Taipei, 110, Taiwan. Fax: +886 2 66395192.

E-mail address: cannilyhuang@gmail.com (P.-S. Huang).

However, she had consciousness change and seizure on the day after admission. Lumbar puncture was performed, which revealed elevated intracranial pressure (300 mmH₂O) with lymphocytic pleocytosis. On day 4 of admission, she became unresponsive and hypoxic, thereby requiring intubation and was hence placed on ventilator care. Her laboratory data and venereal disease screening test were normal. Polymerase chain reaction (PCR) testing failed to detect HSV or VZV DNA. An extensive array of microbiological and serological studies was searched for infectious agents but was negative. Urine drug screen was negative. Brain magnetic resonance imaging (MRI) and angiography (MRA) were unremarkable. Autoimmune antibodies (Abs) examination results were also negative. Treatment with antimicrobial drugs, including acyclovir, ceftriaxone, vancomycin, doxycycline, and oseltamivir, was initiated for the tentative diagnosis of CNS infection.

She became bradycardic and required dopamine treatment to maintain her vital signs. In addition, intermittent generalized myoclonus occurred several times in a day in conjunction with both eyes looking up or becoming disconjugated (oculogyric crises). Anti-epileptic drugs, including levetiracetam, phenobarbital, and clobazam, were then prescribed. Her electroencephalography (EEG) was repeated thrice, but no epileptic-form discharges were noted. However, fluctuating rigidity involving her limbs and trunk was noted, and she would occasionally involuntarily sit up and stare. Methylprednisolone therapy was then initiated, followed by plasma exchange.

Finally, cerebrospinal fluid (CSF) was positive for anti-NMDAR Abs on day 14 of her admission (Fig. 1). Accordingly, she received intravenous immunoglobulin (IVIG) therapy, but her general condition and consciousness continued to worsen. She was then transferred to a medical center, where CT revealed a 2-cm left ovarian teratoma. Thereafter, anti-NMDAR encephalitis associated with teratoma was suspected, and laparoscopic left ovarian cystectomy was arranged at 2 months from the initial presentation.

After surgery, her muscle power and consciousness gradually improved. Tracheostomy was performed owing to the need for prolonged airway access. She could breathe by herself with a tracheostomy collar at 2 weeks after surgery. However, she had difficulty in swallowing, and muscle power of her four limbs was weak. Her ADL function of dressing, toileting, and bathing still needed maximal assistance. Her mobility status showed poor sitting and standing balances of her dynamic and static functions. She required further rehabilitation treatment.

Case 2

The second patient was a 28-year-old nulliparous female who denied any underlying disease and presented with vomiting,

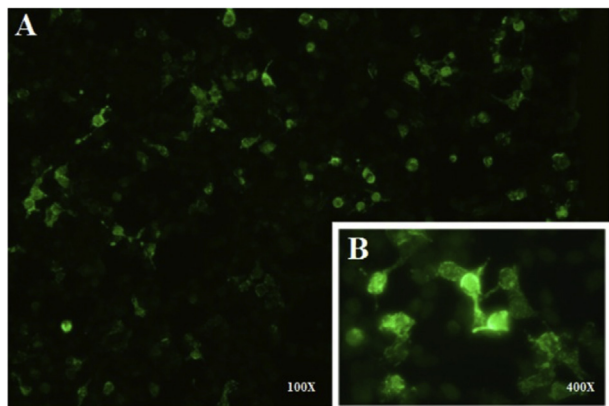


Fig. 1. CSF anti-NMDAR Ab was positive.

confusion, dull response and acute disorientation for 5 days. She also complained of sore throat, malaise and dysuria throughout the previous 2 weeks. She was empirically treated for viral cold symptoms. Then high fever accompanied with urine retention was noted 1 week prior to her admission. At the emergency department, physical examination revealed bilateral costophrenic angle knocking pain. Acute pyelonephritis was suspected, and she was admitted for empiric antibiotic treatment with cefotaxime sodium since April 2, 2017. A gynecologist was consulted for a calcified lesion found on KUB, and her sonography demonstrated a 3-cm right ovarian teratoma.

However, mental status change and generalized tremor were noted on April 4, 2017, and a neurologist was consulted. Her neurological examination revealed no focal signs. Her Glasgow coma scale score was E3V3M5. Her brainstem reflexes were intact. EEG revealed moderate diffuse cortical dysfunction. MRI/MRA showed an equivocal lesion at the splenium of the corpus callosum and mild posterior hemisphere edema. Her laboratory data and venereal disease screening tests were normal. PCR testing also failed to detect HSV or VZV DNA. An extensive array of microbiological and serological studies was searched for infectious agents, but all were negative. Urine drug screen was also negative. CSF analysis revealed elevated protein level with monocyte predominant leukocytosis and decreased glucose level, which favored viral or tuberculosis (TB) meningitis; therefore, antimicrobial treatment (comprising ceftriaxone and acyclovir) and anti-TB medication were prescribed since April 6, 2017. Dexamethasone was also added for brain edema.

Her condition progressed despite drug treatment, and she was transferred to our hospital on April 9, 2017. On admission, she had mild fever (38.5 °C) and sudden consciousness disturbance with yelling and making faces. Her abdominal CT revealed a 3.3-cm teratoma with calcification of the right ovary (Fig. 2). Methylprednisolone therapy was initiated, followed by plasma exchange, with mild improvement of language and cognitive functions. The confirmation of clinical diagnosis of anti-NMDAR encephalitis requires a positive serum or CSF sample screening for Abs to the NMDA receptor. However, this test was unavailable in our hospital. Because of a high suspicion of anti-NMDAR encephalitis associated with ovarian teratoma that was rapidly progressing to autonomic



Fig. 2. Fat containing lesion at right ovary up to 3.04 cm with calcified dot, ovarian teratoma is considered.



Fig. 3. Surgical finding showing (A) Normal appearance of left ovary. (B) Right ovarian teratoma. (C) Appearance of right remaining adnexa after cystectomy.

instability and respiratory distress, laparoscopic right ovarian cystectomy was performed without laboratory confirmation on April 24, 2017 (Fig. 3). Within 24 h after surgery, a marked improvement in her cognitive function was noted. Final histopathology confirmed the diagnosis of a mature teratoma (Fig. 4). With supportive treatment and intense rehabilitation therapy, she showed good recovery, except for recurrent urinary retention.

Discussion

Anti-NMDAR encephalitis was first described by Dalmau et al., in 2005 [1]. Anti-NMDAR Abs present in the serum or CSF is an important clinical feature [1]. NMDA receptors play a vital role in neural transmission of synaptic function, which may be disturbed by anti-NMDAR IgG to the NMDA receptor glutamate subunit, thereby causing various neuropsychiatric symptoms [2].

Anti-NMDAR encephalitis usually occurs among young women and is often associated with ovarian tumors, specifically teratomas [2]. Dalmau et al. [2] reported that 58 of 98 (59%) patients had a neoplasm. In a multi-institutional observational study [3], 207 of 577 (36%) patients had tumors, and 94% of all tumors were ovarian teratomas. In our study, of 13 patients with anti-NMDAR encephalitis, six had ovarian tumors, and five of those were ovarian teratomas (Table 1).

Clinical features of anti-NMDAR encephalitis are severe and potentially life threatening (Table 1). Anti-NMDAR encephalitis often occurs initially with non-specific flu-like symptoms. In our review, nine anti-NMDAR encephalitis cases were initially diagnosed and managed as flu. Psychiatric manifestations, such as agitation, delusions, hallucinations, and anxiety and behavioral change, may gradually present within several weeks in such cases

[4]. Typically, the disease abruptly progresses to memory deficit, irritable behaviors, autonomic instability, seizures, muscle rigidity, facial dyskinesia (dysautonomia), and hypoventilation. In such a scenario, patients are admitted to the ICU and provided ventilator support when life-threatening neurological deterioration occurs.

Workup was initiated to eliminate infective encephalitis. The diagnosis of encephalitis associated with teratomas is time-consuming and difficult [5]. As demonstrated in our patients, CSF study, EEG, and MRI may show non-specific findings. Although neurological symptoms present as severe, tumors may be extremely small and difficult to detect on imaging. We believe that a focused transvaginal or transrectal ultrasound should be the first-line test for diagnosing ovarian teratomas because it is safe, inexpensive, and provides satisfactory sensitivity and positive predictive values. Ultrasound is often the initial imaging study of choice, followed by CT for inconclusive cases.

The present literature review suggests that the combination of tumor resection and immunotherapy (IVIG, corticosteroids, and plasma exchange) yields the best therapeutic results and a more rapid recovery than immunotherapy alone [3,6,7]. In case of immunotherapy, corticosteroid (i.e., methylprednisolone) and IVIG administration, or sometimes plasma exchange, show good outcomes.

Tumor resection has been recommended as first-line treatment for anti-NMDAR encephalitis with positive tumor findings [3,6,7]. The most common tumors associated with anti-NMDAR encephalitis are ovarian teratomas containing neural tissues expressing NMDA receptor [2]. Insufficient previous data were retrieved on tumor size and its relation to the disease. In the review of anti-NMDAR encephalitis with mature teratoma, mean tumor size was 6.7 ± 5.7 cm (range, 1–22 cm) [5]. In our cases, the tumor sizes of the teratomas were 2.0 and 3.3 cm.

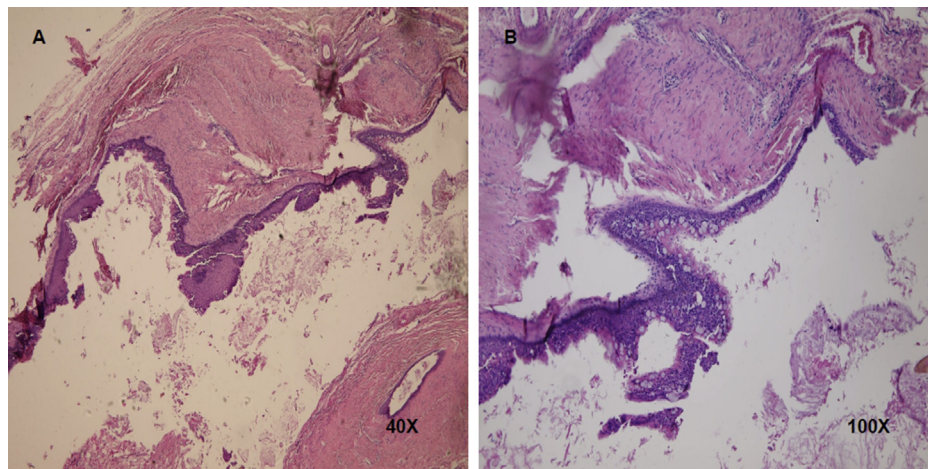


Fig. 4. Sections show mature teratoma composed of a cystic lesion filled with sebaceous material, lined by squamous epithelium with skin appendages and presence of mature bone tissue. (hematoxylin-eosin stain; original magnification, A×40, B×100).

Table 1

Clinical features of the 13 female with Anti-NMDAR encephalitis in Taiwan.

Case No	R.	Age	Prodromal symptoms	Neuropsychiatric Symptoms	Autonomic Dysfunction and Hypoventilation	Ov. tumor pathology, size	Time to dx, hospitalization	Primary therapy	Outcome
1	Hung et al. (2011) [9]	14	Headache, dizziness, no fever	Mood lability, hallucination, mute, memory deficit, OCD, decreased consciousness, and seizure (GTC)	Insomnia, hypotension, and excessive sweating	—	—	MP, IVIG	Substantial improvement (mo)
2	Kuo et al. (2012) [10]	16	Fever, cough, rhinorrhea	Inappropriate laughing and sang loudly, agitation, bizarre behavior, hallucination, change in consciousness, and seizure (clonic)	Difficulty sleeping, hyperthermia, tachycardia, hypoventilation*	—	—	MP, IVIG	Lower limb weakness and slow speech
3	Dou et al. (2012) [11]	26	fever and headache	dystonic posturing, oro-lingual-facial dyskinesias, and myoclonic movements	Hyperthermia, Hypoventilation+	—	—	MP, PE, IVIG	Substantial improvement (mo)
4	Hsu et al. (2013) [12]	7	—	Intractable seizure, severe SIADH, aggressive behaviors, talkative, headache, dyskinesia, mutism, hypoventilation	Hypoventilation+	MT, —	60 days, 89 days	Tumor resection	Mutism; limited improvement (1 yr)
5	Hsu et al. (2013) [12]	14	—	Hallucination, depression, dyskinesia, hypoventilation, headache, hypersalivation, mutism	Hypoventilation+, hypersalivation	MT, —relapse 2 years later	21 days, 53 days	Tumor resection, IVIG, MP	# Substantial improvement (3 yr)
6	Lin et al. (2014) [13]	15	Anorexia and nausea	Seizure (GTC), agitation, mood lability, decreased consciousness, and hallucination	Hyperthermia, difficulty sleeping, hypertension, urine retention	—	—	MP, IVIG	Substantial improvement (5 mo)
7	Lin et al. (2014) [13]	20	—	Decreased consciousness, agitation, seizure (focal), mood lability, disorientation, hallucination, and aphasia	Insomnia, hyperthermia, sweating, dilated pupils, hypoventilation**	—	—	PE, MP	Substantial improvement (3 mo)
8	Lin et al. (2014) [13]	23	—	Agitation, mood lability, hallucination, seizure (GTC), decreased consciousness, impaired speech, and memory deficit	Insomnia, hyperthermia, tachycardia, urine frequency, difficulty sleeping	—	—	MP	Limited improvement (4 yr)
9	Lin et al. (2014) [13]	24	Fever, nausea, and headache	Mood lability, disorientation, impaired speech, and seizure (focal)	Urine retention, hypoventilation*, and tachycardia	—	—	PE, MP	Substantial improvement (3 mo)
10	Lin et al. (2014) [13]	28	Cough, rhinorrhea, and no fever	Decreased consciousness, mood lability, hallucination, impaired speech, disorientation, and seizure (GTC)	Hypertension, tachycardia and/or bradycardia, urine retention, ileus, hypothermia, and hypoventilation*	Ov fibroma, —	30 days, —	Tumor resection, MP, PE, IVIG, cyclophosphamide	Limited improvement (2 yr)
11	Lee et al. (2016) [14]	17	Fever, dizziness and transient loss of consciousness	Decreased consciousness, psychosis, refractory seizures, hyperkinesia, complex partial status epilepticus	hyperthermia, tachycardia, and hyper-salivation.	MT, —	150 days, 210 days	Oophorectomy, MP, PE, IVIG, Rituximab	Limited improvement (1 yr)
12	Present study (2018)	27	poor appetite, headache, general malaise and fever	Decreased consciousness, mood lability, hallucination, impaired speech, disorientation, and seizure (GTC)	Tachycardia, urine retention, hyperthermia, and hypoventilation*	MT, 2.0 cm	60 days, 90 days	Tumor resection, MP, PE, IVIG	Limited improvement (2 yr)
13	Present study (2018)	28	sore throat, malaise and dysuria	Decreased consciousness, generalized tremor, impaired speech, disorientation	hypothermia, urine retention	MT, 3.3 cm	7 days, 37 days	Tumor resection, MP, PE, IVIG	Substantial improvement (1 yr)

Abbreviations: Ov = ovarian; dx = diagnosis; BiPAP = Biphasic positive airway pressure; GTC = Generalized tonic-clonic; NMDA = N-methyl-D-aspartate; OCD = Obsessive compulsive disorder; * Hypoventilation with intubation; ** Hypoventilation with BiPAP use; +No mention of treatment; MT = mature teratoma; IVIG = Intravenous immunoglobulin; MP = Methylprednisolone; PE = Plasma exchange; # Remitted at 2 months, recurrent dyskinesia 2 years later, and remitted 1 month after tumor removal.

Gynecologists should be aware of the presence of tumors in anti-NMDAR encephalitis patients. Even for small tumors, surgical resection is essential because it speeds up the improvement and decreases chances of a relapse. Dabner et al. [8] described a case wherein bilateral oophorectomy was performed, despite negative scan results, which improved clinical symptoms, and the final pathology revealed a 0.7-cm mature teratoma. We believe that oophorectomy or cystectomy for teratoma is beneficial in anti-NMDAR encephalitis patients.

Titulaer et al. [3] reported that good outcome predictors include a lower symptom severity (assessed as no need for admission to the ICU), prompt immunotherapy initiation, and tumor resection, which conforms to our review that the sooner the tumor is resected, the better is the prognosis. In our study (Table 1), two patients with substantial clinical improvement (case 5 and 13) had shorter time to diagnosis of teratoma. All patients with teratomas demonstrated obvious improvement in their clinical conditions after tumor resection, even if they were previously resistant to the immunotherapy.

In addition, once anti-NMDAR encephalitis is clinically suspected among patients with behavioral and/or neurological changes, ovarian tumors and NMDA receptor Abs should be evaluated, even in patients with unremarkable CSF and MRI findings. Subsequent tumor removal, in addition to diagnostic confirmation through the presence of anti-NMDAR Abs, must be emphasized.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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