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Anti-NMDAR encephalitis with delayed ovarian teratoma in a young woman: a case report with 5 years of follow-up

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Abstract

Background Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder with a variety of clinical manifestations. It has been established that anti-NMDAR encephalitis may be related to ovarian teratoma in female patients. However, a considerable number of patients have no obvious evidence of ovarian teratoma during the onset of the disease.

Case A 25-year-old previously-healthy female experienced a series of acute symptoms within two days, including confusion, disorientation, short-term memory loss, auditory hallucinations, abnormal behavior, refractory status epilepticus, etc. Her brain MRI and abdominal imaging showed no definite abnormality while her electroencephalogram exhibited the presence of low to moderate amplitude sharp, spike, and multi-spike waves. Serum and cerebrospinal fluid tests yielded positive results for anti-NMDAR antibodies. However, an ultrasound scan failed to identify an ovarian teratoma. Consequently, the diagnosis of anti-NMDAR encephalitis without teratoma was made after 4 days onset. After the plasma exchange and immunoglobulin therapy, her neurological symptoms improved and obtained a clinical cure. In the next eight months of follow-up, the patient accidentally touched a lump in the lower abdomen without any symptoms, and abdominal ultrasound and CT scan revealed a left ovarian tumor. Then she underwent left ovarian teratoma resection surgery and histopathology showed a mature cystic teratoma with neural components. The patient continued to receive five years of follow-up, and her condition remained stable without any recurrence, except that there had been a low titer of anti-NMDAR antibody in her serum.

Conclusion Our case demonstrated the importance of long-term follow-up for female patients with anti-NMDAR encephalitis, since anti-NMDAR encephalitis-associated ovarian teratomas may develop in a delayed manner, even without any symptoms.

Keywords Anti-NMDAR encephalitis, Anti-NMDAR antibodies, Ovarian teratoma, Follow-up

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Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is one of the most common causes of autoimmune encephalitis, with an annual incidence of 1.5 per million [1]. The disease usually presents with psychiatric, neurological, and autonomic symptoms, often accompanied by viral prodromes [2]. It is noteworthy that anti-NMDAR encephalitis is associated with ovarian teratomas in females [3]. In approximately 60% of cases, the presence of mature ovarian teratomas co-occurs with anti-NMDAR encephalitis [4, 5]. Therefore, it is important to detect ovarian masses in the diagnosis of anti-NMDAR encephalitis. Early tumor resection followed by symptomatic immunotherapy could reduce the risk of recurrence and even lead to full recovery [6] .

Nevertheless, it is notable that a considerable number of patients diagnosed with anti-NMDAR encephalitis have no discernible evidence of ovarian teratoma at the time of disease onset. In this case, we present the definitive diagnosis of anti-NMDAR encephalitis in a young female patient, despite the initial absence of tumors markers. Following the administration of symptomatic immunotherapy, the patient was deemed to have achieved a clinical cure. However, over the course of an eight-month follow-up period, an ovarian cystic teratoma developed in this patient. Following surgery, the patient's condition remained stable without any recurrence over the subsequent five-year follow-up period, with the exception of the persistent existence of a low titer of anti-NMDAR antibody in her serum. It is therefore imperative to emphasize the necessity of long-term follow-up for female patients with anti-NMDAR encephalitis, given that the development of ovarian teratomas may occur at a delayed stage.

Case report

A 25-year-old previously-healthy woman was admitted to the hospital on March 4, 2019, after presenting with acute symptoms over the previous two days. These included confusion, disorientation, impaired short-term memory, insomnia, auditory hallucinations, and aberrant behaviors. There was no history of fever over the previous two weeks. On admission, her vital signs were within normal limits, her pupils were of normal size and reactive to light, her other cranial nerve functions were intact, and her strength of all limbs was 5/5. All deep tendon reflexes were brisk, and bilateral plantar reflexes showed a withdrawal response. She exhibited neither nuchal stiffness nor pathological reflexes. She was disoriented and presented severe anterograde amnesia. On the first night of hospitalization, she experienced several generalized seizures and a notable decline in consciousness. Subsequently, she developed status epilepticus and hyperthermia, and then was transferred to the ICU. Despite treatment with antiepileptic drugs, the generalized seizure was difficult to control. This resulted in hypoventilation, leading to tracheal intubation and artificial ventilation.

Her total leukocyte count was 6.83×10^9 cells/L (neutrophils 90.8%, lymphocyte 8.5%), hemoglobin 98 g/L, blood urea nitrogen 2.78 mmol/L, creatinine 32 μmol/L, sodium 141 mmol/L. β-HCG, alpha fetoprotein, antinuclear antibody, and Rh factor were negative. The cerebrospinal fluid (CSF) analysis revealed an elevated pressure of 200 mmH_2O, accompanied by a lymphocytic pleocytosis (71 WBCs, 90% lymphocytic), with normal protein and glucose levels and negative oligoclonal bands (March 4, 2019). The thyroid function test yielded normal results. The ultrasound examination of the abdomen and pelvis did not reveal any evidence of a tumor lesion (Fig. 1A). The brain MRI was unremarkable. A chest and abdomen CT scan revealed no abnormalities. Two electroencephalogram (EEG) examinations were performed within one week after admission (on March 4 and 8, 2019), which showed the presence of low to moderate amplitude sharp, spike, and multiple spike waves distributed bilaterally in the prefrontal, frontal, temporal lobes of the patient's brain (Supplementary Figs. 1 and 2).

Based on above examinations, a tentative diagnosis of viral encephalitis was made and then intravenous acyclovir was initiated. In the following day, symptoms gradually develop into involuntary movements, including pouting, chewing, and leg cycling. Therefore, a diagnosis of autoimmune encephalitis was suspected, and then the patient was treated with glucocorticoids on March 5, 2019. The specific regimen was as follows: three consecutive days of intravenous injection of 1000 mg methylprednisolone, followed by three consecutive days of injection of 500 mg, and finally three days of injection of 250 mg. On the second day of glucocorticoid treatment (March 6, 2019), a cell-based indirect immunofluorescence assay revealed the presence of antibodies against the NMDAR in both serum (1:100) and CSF (1:320) (Supplementary Figs. 3 and 4), and then the diagnosis of anti-NMDAR encephalitis was confirmed. Subsequently, intravenous immunoglobulin (IVIG) was initiated on the 4th day (March 6, 2019) after disease onset at a dose of 0.4 g/kg for five consecutive days. However, her condition deteriorated, developing into severe pneumonia, high fever, and unstable ventilation. On March 22, 2019, the EEG showed non-specific slow waves (Supplementary Fig. 5). Thus, tracheotomy and mechanical ventilation were performed. Plasmapheresis was performed on the 30th day after admission. Two weeks later, her pneumonia was resolved, her temperature returned to normal, and she no longer had seizures. Repeated examination of EEG showed no abnormalities on April 12, 2019. The IVIG was reintroduced at a dose of 0.4 g/kg for a period

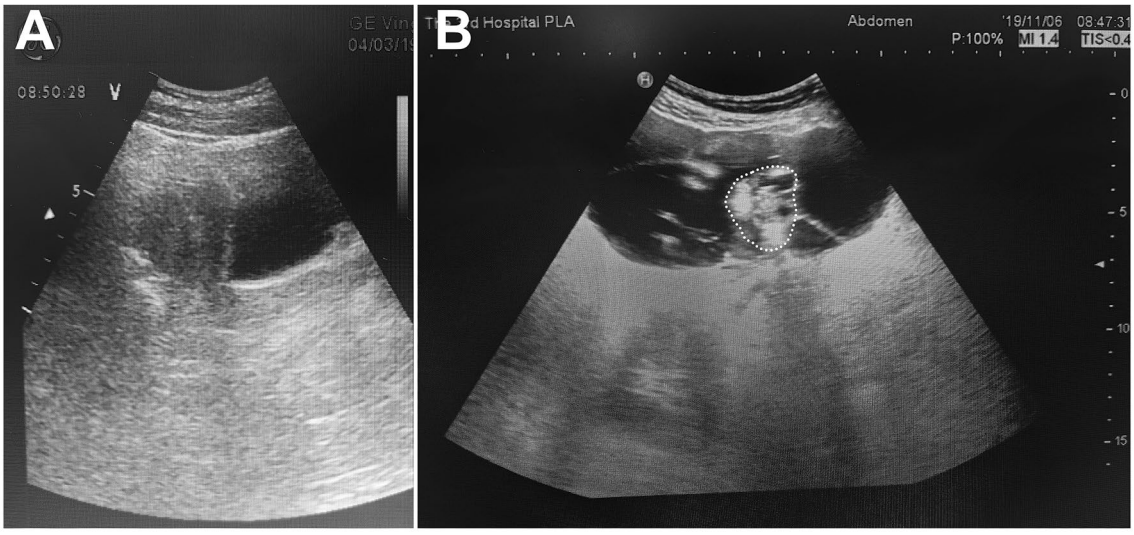

Fig. 1 Abdominal ultrasound findings of the patient at onset and 8 months after onset of the disease. (**A**) At onset (March 4, 2019), abdominal ultrasound showed no abnormality. (**B**) Eight months later (November 6, 2019), abdominal ultrasound showed a 12.7 cm x 8.9 cm cystic echogenic area in the left adnexal region with an irregular morphology and a well-defined border (dashed circle). The contents were predominantly fluid with a clear separation between the bright band and the echogenic area

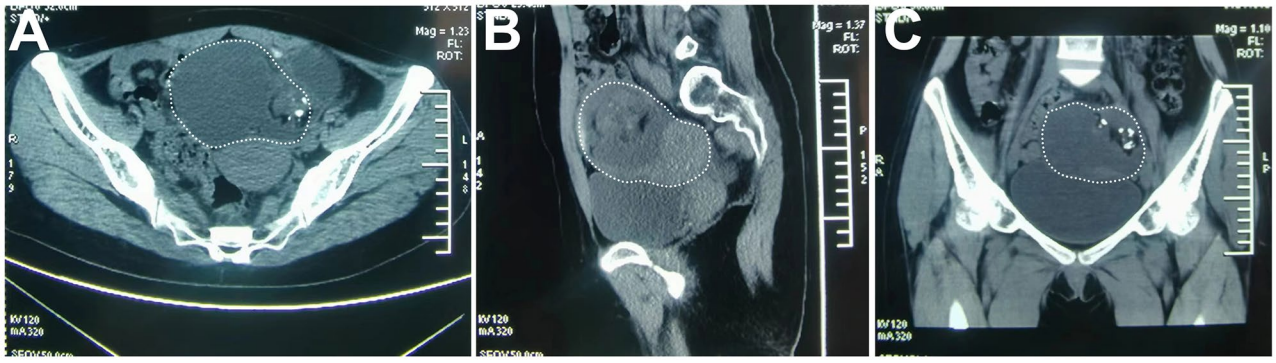

Fig. 2 A focal space-occupying lesion revealed by Pelvic CT scan. A rounded low-density nodule was showed in the lower left pelvis on horizontal (**A**), coronal (**B**) and sagittal (**C**) CT scan (dashed circles)

of five days, on the 52nd day of admission. Subsequently, remarkable clinical improvement was observed, with gradual resolution of involuntary movement symptoms. However, residual psychiatric symptoms (alert, intermittent agitation, and spontaneous speech), amnesia and cognitive impairment remained. The patient was discharged on the 66th day of admission with stable condition, and was instructed to continue taking prednisone orally following their discharge. Over time, her psychiatric abnormalities, cognitive function, and involuntary movements demonstrated gradual improvement. Approximately seven months after the initial onset of symptoms, the patient had fully recovered and was able to resume her occupational duties with no remaining impairment.

In the eighth month after the onset, the patient made contact with a lump in the lower abdomen, the presence of which was not accompanied by any symptoms. Abdominal ultrasound showed the presence of a substantial cyst measuring 12.7 cm × 8.9 cm in left adnexa (Fig. 1B, dashed circle). A subsequent pelvic CT scan revealed a focal space-occupying lesion (12.4 cm × 7.4 cm × 8.4 cm) with low fat density in the left lower pelvis (Fig. 2, dashed circles). Finally, she underwent a left ovarian resection, during which a regular cyst with a smooth surface was discovered (Fig. 3A). Following incision, the cyst was found to contain a variety of tissues, including hair and bone (Fig. 3B), which are consistent with the characteristics of a mature ovarian teratoma. A subsequent histopathological examination revealed that the specimen exhibited features consistent with a mature cystic teratoma comprising components of the epidermis, bone, cartilage, and nervous system (Fig. 4). Nevertheless, there was a notable absence of lymphocytic infiltrate within the neuroglial tissue (Fig. 4D and E). The patient was discharged on the ninth postoperative day.

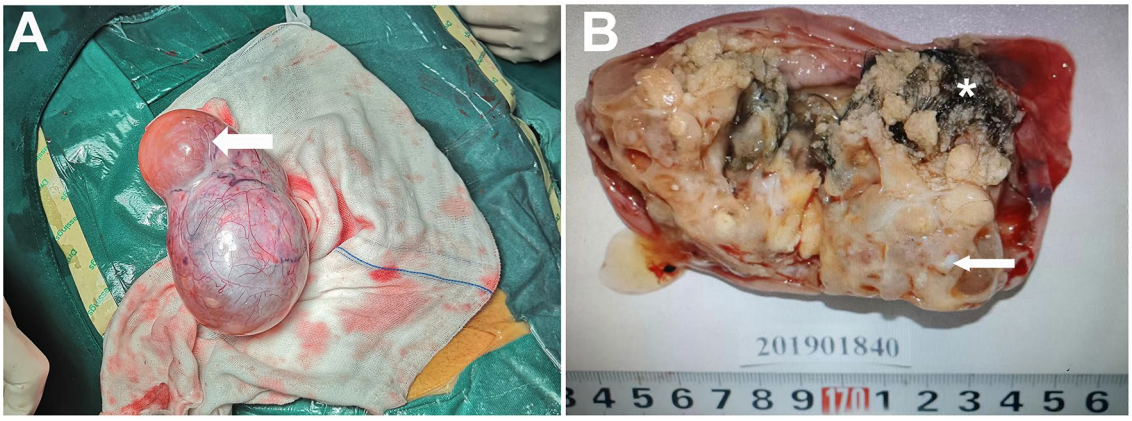

Fig. 3 A teratoma in the ovary. (**A**) Intraoperative morphology of the left ovary with a regular cyst with smooth surface (white arrow) was showed. (**B**) The cyst contained various tissues, such as hair (white asterisk) and bone (white arrows) after incision

In the next five years of follow-up, the patient had no residual after-effects and her condition had not recurred. Her menstrual cycle was regular and no abnormalities were found on ovarian ultrasound. However, after four years of the onset, her serum was still positive for anti-NMDAR antibodies at a low titer (1:10) on December 7, 2023 (Supplementary Fig. 6).

Discussion

Anti-NMDAR encephalitis is defined as an immune-mediated disease characterized by a series of complex neuropsychiatric syndromes and the presence of CSF or serum antibodies against the GluN1 subunit of the NMDAR receptor [1, 4]. The disease may manifest in a variety of ways, with symptoms including psychiatric or cognitive impairment, seizures, speech dysfunction, movement disorders, decreased consciousness levels, autonomic dysfunction or central hypoventilation [2]. Anti-NMDAR encephalitis may be associated with various tumors, such as malignant tumor, mediastinal teratoma, small cell lung cancer, or ovarian teratoma [7]. The initial report of the relationship between anti-NMDAR encephalitis and ovarian teratoma was published in 2007 [8]. It has been estimated from case reports and observational studies that 36-50% of female patients with anti-NMDAR encephalitis may have ovarian teratomas [9]. Ovarian teratoma was predominantly observed in adolescent and adult patients [10]. In women over the age of 18, the incidence of ovarian teratoma in conjunction with anti-NMDAR encephalitis is 56%, with a decline in prevalence with age [10]. Teratomas from patients with anti-NMDAR encephalitis almost universally contain nervous tissue [4, 11–15], which expresses NMDA receptor [4, 12], in contrast to those from non-encephalitic patients [4, 12–14]. Furthermore, nervous tissue present in anti-NMDAR encephalitis teratomas is more likely to contain histological features of glial tumors [13], dysplastic neurons [14] and higher proliferative indices [16].

Previous studies have indicated that anti-NMDAR autoantibody titers may reflect the progression of clinical disease [4, 17–19]. Specifically, higher antibody levels in serum or CSF have been associated with more adverse outcomes on the Modified Rankin Scale (MRS). The antibody titers are usually higher in serum than in CSF [18, 20]. Additionally, patients with underlying teratoma may exhibit elevated serum titers [4, 18, 19]. Conversely, the fluctuations in antibody levels within the CSF during a relapse may be more indicative of clinical activity than those observed in serum. Furthermore, a reduction in CSF antibody levels in the early stages of the disease may be associated with a favorable prognosis in the future [21]. Nevertheless, the majority of patients remain seropositive for anti-NMDAR antibodies in both serum and CSF following clinical recovery [22]. Similarly, our case demonstrates that the patient exhibited elevated antibody titers in both CSF and serum during the rapid progression of the disease, while antibody levels in the serum remained low four years after full recovery.

In patients with ovarian teratoma-associated encephalitis, immunomodulatory methods have been proved to be the primary supportive and therapeutic options for the elimination of underlying causes and risk factors [23]. Most patients will benefit from immunotherapy. However, immunosuppressive treatment in isolation is an inadequate strategy for achieving a cure [24]. In contrast, complete resection of the teratoma could prove curative. Nevertheless, it has been demonstrated that the most effective approach is a combination of surgical intervention and immunotherapy, which can achieve the optimal clinical response and facilitate complete recovery [23]. Even in cases where the teratoma has reached an advanced stage of the disease, its removal can still be therapeutic [25]. Consequently, the early detection and surgical removal of ovarian teratomas during immunotherapy are of paramount importance.

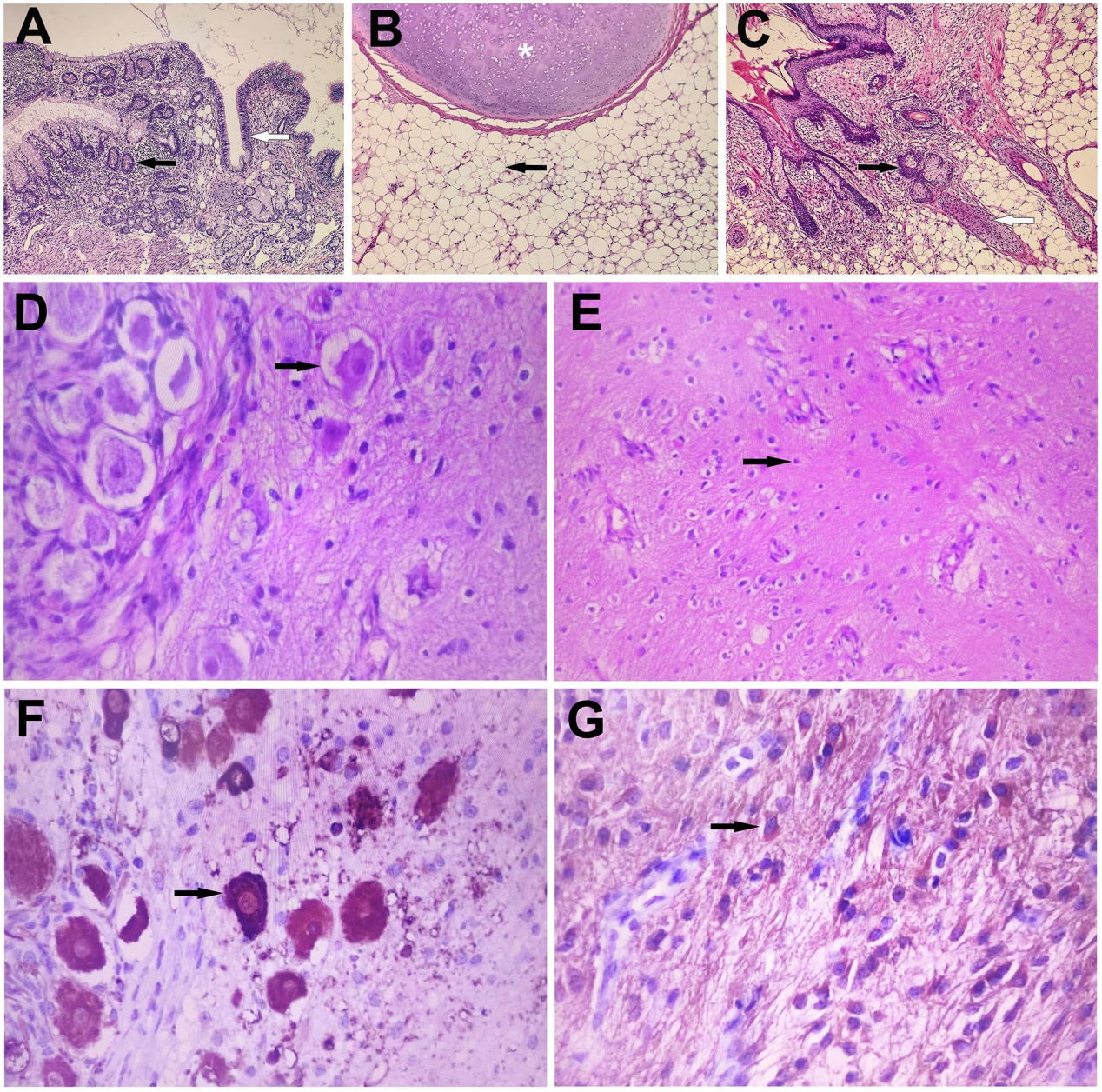

Fig. 4 Histological and immunohistochemical staining of teratoma. (**A**-**E**) Histological staining of the cystic mass revealed features of the endoderm (**A**), such as respiratory epithelium (white arrow) and digestive epithelium (black arrow), the mesoderm (**B**), such as cartilage (white asterisk) and fat (black arrow), and ectoderm (**C**-**E**), such as sebaceous glands (black arrow in C), hair follicles (white arrow in C), and neuronal (black arrow in D) and glial components (black arrow in E) of tumor. Note that no significant lymphocytes are observed in the neuroglial tissue. The magnification in panels (A-E) is 100 x. Immunohistochemical staining showed that immunoreactivities of NSE (**F**) and GFAP (**G**) were present in the tumor tissue. Arrows show typical NSE- and GFAP-positive cells, respectively. The magnification in panels (**F** and **G**) is 400x

There have been several reports of recurrent ovarian teratomas with autoimmune encephalitis and encephalitis after teratoma surgery. Muni et al. [26]. reported a case of a young woman with a history of recurrent benign ovarian teratoma who presented with recurrent central nervous system symptoms. After surgical resection of the teratoma and combined treatment with corticosteroid and IVIG, all neurological symptoms exhibited a rapid improvement. In a separate case study, Brian K. et al. [27] presented a case of a young woman diagnosed with NMDAR encephalitis several months after undergoing surgical removal of an ovarian teratoma. However, approximately 80% of tumors are diagnosed concurrently with the onset of encephalitis, 4.1% are diagnosed before the onset of encephalitis, and only about 15% of patients are diagnosed after a protracted recovery from

encephalitis [28–30]. In some instances, the teratoma was only identified following oophorectomy [31] or autopsy [32]. However, in our case, high titers of anti-NMDAR antibodies were present at an early stage of the disease, and there was no obvious evidence of teratoma at that time. Following the administration of symptomatic immunotherapy for a period of eight months, during which time a clinical recovery was achieved, a large ovarian teratoma became apparent. We supposed that in the early stages of disease, the volume of tumor may be insufficient to be detected by conventional abdominal ultrasound and CT scan. Despite its minute dimensions, the tumor may be in an active state at this stage, prompting the body to produce a substantial quantity of anti-NMDAR antibodies. Consequently, our case study underscores the necessity for prolonged follow-up of patients diagnosed with anti-NMDAR encephalitis, as teratomas may manifest with a delay.

Some research has demonstrated a notable disparity in the inflammatory infiltrates of B cells, T cells and mature dendritic cells between anti-NMDAR encephalitis-associated teratomas and non-NMDAR teratomas in the presence of neural elements [13]. Amber N et al. [33] demonstrated that anti-NMDAR encephalitis-associated teratomas exhibited distinctive gross pathological features, with neuroglial tissue and lymphoid follicles predominantly located in the Rokitansky nodes, which are more common than mature non-NMDAR teratomas. Additionally, several studies have showed that anti-NMDAR encephalitis-associated ovarian teratomas have dense inflammatory infiltration around the neural tissue [12, 16, 34]. However, in our case the ovarian teratoma contained bone, cartilage, epidermal and neuroglial tissue, which however, was not surrounded by abundant lymphocytes. This may be attributed to the fact that the inflammatory infiltration was significantly attenuated by early symptomatic immunotherapy.

Currently, only a few studies have directly compared the clinical features of anti-NMDAR encephalitis with and without ovarian teratoma. In a retrospective study of 108 patients with anti-NMDAR encephalitis, Dai et al. [35] found that the patients with ovarian teratomas exhibited more severe clinical symptoms at onset, higher MRS, and a higher mortality rate than those without ovarian teratomas. Inconsistently, Zhang et al.'s study reached a different conclusion [36], claiming that the patients with anti-NMDAR encephalitis combined with teratomas present with milder neurological symptoms. Meanwhile, they also found that patients with ovarian teratoma displayed fewer viral prodromes but higher levels of anti-NMDAR antibodies in the CSF while nontumor patients had lymphocytic pleocytosis in the CSF, indicating that tumor may be the immunologic trigger for anti-NMDAR encephalitis patients while viral infection may play a role in pathogenesis for nontumor patients [36]. Consistently, both studies above and our case showed that the removal of ovarian teratomas is associated with reduced risk of relapse or better long-term outcomes. In addition, Desestret and colleagues [37] evaluated the presence of IgA subtype of anti-NMDAR antibodies in the CSF of patients with anti-NMDAR encephalitis, and found that 49% of the IgA-NMDAR-antibody-positive patients definitively had associated tumors, primarily ovarian teratomas (94%), compared with only 5% of the patients in the IgA-NMDAR-antibody-negative group, indicating CSF IgA-NMDAR antibodies may be served as a biological marker for the presence of an ovarian teratoma. This finding also highlights the importance of detecting IgA-NMDAR antibodies, especially for the patients without tumor signs in the early stage of anti-NMDAR encephalitis, just as in our case.

In 1997, Benjamin Caspi et al. [38] conducted a prospective observational study to analyze the growth patterns of ovarian dermoid cysts in premenopausal and postmenopausal women. The study revealed that the average growth rate of dermoid cysts in premenopausal women was 1.8 millimeters per year. It is noteworthy that a 25-year-old female patient of childbearing age in our study developed a large mature teratoma measuring 12 centimeters over the span of eight months, a phenomenon that is exceptionally uncommon.

Conclusion

In young female patients with acute psychiatric symptoms and seizures, anti NMDAR encephalitis should be suspected and the teratoma should be searched for thoroughly. Even if there are no signs of ovarian teratoma at the time of symptom onset, long-term follow-up should be conducted in order to discover delayed ovarian teratoma.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-024-03891-x.

Supplementary Material 1: Supplementary Figure 1. The results of patient's EEG on March 4, 2019. The results demonstrated the presence of low to moderate amplitude sharp, spike, and multiple spike waves distributed in the left frontal and left anterior middle temporal regions of the patient's brain.

Supplementary Material 2: Supplementary Figure 2. The results of patient's EEG on March 8, 2019. The results demonstrated the presence of a limited number of paroxysmal, 6-8 second, medium-high amplitude 1.5-2.5 Hz theta waves, which exhibited overlapping characteristics with low-amplitude fast waves, akin to δ-brushes. These were observed in the patient's left prefrontal, frontal, and central leads. The right anterior and middle temporal conductors displayed several paroxysms of medium-high amplitude spike wave complexes, with a duration of 1-6 seconds.

Supplementary Material 3: Supplementary Figure 3. The results of anti-NMDAR antibodies in the patient's serum on March 5, 2019.

Supplementary Material 4: Supplementary Figure 4. The results of anti-

NMDAR antibodies in the patient's CSF on March 5, 2019.

Supplementary Material 5: Supplementary Figure 5. The results of patient's EEG on March 22, 2019. The results demonstrated the presence of non-specific slow waves across the entire conductance of the patient's brain.

Supplementary Material 6: Supplementary Figure 6. The results of anti-NMDAR antibodies in the patient's serum on December 9, 2023.

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Author contributions
H.L.X(Hailong Xue) and J.H.H(Junhao Hu) were responsible for study design and concept. Y.G.C(Yingge Chen), W.B.H(Wenbin Huang), H.L.L(Haoling Liu) and H.L.X(Hongli Xu) were involved in data acquisition. M.S(Ming Shi) revised the manuscript. All authors contributed to the article and approved the submitted version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This report was written in compliance with the Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. In accordance, written informed consent was obtained from the legal guardian of the patient.

Consent for publication
Written informed consent to publish this case report was provided by the patient.

Competing interests
The authors declare no competing interests.

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