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Case Report

Anti N-Methyl-D-Aspartate Receptor Encephalitis with Ovarian Teratoma: A Dilemma in Diagnosis

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Abstract

We report a rare case of altered mental status in a young patient with immature ovarian teratoma. A 22-year-old woman presented with seizures, hallucination, amnesia and orofacial dyskinesia. Examination and investigation revealed an ovarian massand asalphing-oophorectomy was performed. The histopathological examination result showed an immature teratoma grade 2 with thepresence of immature primitive glial tissue. Her CSF N-Methyl-D-Aspartic acid receptor (Anti-NMDAR) antibodytest was positive. N-Methyl-D-Aspartic acid receptor antibody associated limbic encephalitis is an autoimmune antibody-mediated neuropsychiatric disorder. Resection of the tumour and immunotherapy resulted in full recovery.

Keywords: Anti-N-Methyl-D-Aspartate receptor, encephalitis, ovarian tumour, psychosis, teratoma

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Introduction

Anti N-Methyl-D-Aspartate (NMDA) receptor encephalitis is a unique entity that described asyndromewith acute onset of psychiatric symptoms and neurologicalassociation with ovarian teratoma. Despite the fact that it has been recognized for past few decades, the cause is still not well understood. It is however seen more common in young women (1). We report a case of anti-NMDA receptor encephalitis with immature teratoma and illustrate the importance of early diagnosis and prompt surgical removal of tumour that resulted in a full recovery.

Case Report

A previously healthy 22-year-old Chinese female had developed fever and myalgia after jungle trekking a week before admission. There was no known history of drug or alcohol used before. She was brought to hospital after an episode of generalized tonic-clonic seizure. Her vital signs were stable and clinical examination was unremarkable. Urine toxicology was negative and an urgent CT brain imaging did not reveal any abnormality. Her cerebrospinal fluid (CSF) pressure was normal and analysis revealed normal level glucose and protein. CSF investigation with Indian ink was negative and bacterial culture yielded no growth. Screening for viral encephalitis, blood culture and mycoplasma serology were negative. The initial provisional diagnosis of meningoencephalitis was made and she was started on intravenous (IV) ceftriaxone and acyclovir. She was also given anticonvulsant drugs, diazepam and phenytoin.

After two days, she started to have myoclonic jerk at her lips and upper limbs. She was prescribed for oral levetiracetam 250mg twice daily. Apart from this, she experienced auditory hallucinations. She was thought to have a non-epileptic attack disorder as her seizure

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semiology was atypical, consisting of bilateral upper limbs waving movement with preserved consciousness. Her EEG recording was normal at this point. A psychiatric team evaluation further assessed her to have ongoing personality vulnerability.

Subsequently, she had another two episodes of generalized tonic clonic seizures. Her antiepileptic medications were changed to oral sodium valproate 400mg twice daily and intravenous levetiracetam 500mg twice daily. A second EEG was done and revealed slowing at the right hemisphere with epileptic discharges at right temporal lobe. She was noticed to have orofacial dyskinesia affecting her left face. She was then treated for limbic encephalitis and started on pulsed intravenous methylprednisolone 500mg daily for 3 days, and followed by oral prednisolone.

Investigation for malignancy with MRI brain was unremarkable. However a lower abdominal mass was also noted clinically at that point. A transabdominal ultrasound revealed a cystic pelvis mass and a CT scan of the abdomen pelvis confirmed a complex cystic pelvic mass, arising from right ovary with no evidence of distant metastasis. Her tumuor markers revealed slight elevation in CA 19-9 and Alfa-Fetoprotein, results as follows: CA 19-9 149 U/mL (N: <37), Alfa-Fetoprotein 15.71 ng/mL (N: 0.00-6.72), CA 125 34 U/mL (N: 0-35), CEA 1.5 ng/mL (N: 0-3.0), Beta-hCG<1.2 mIU/mL (N: <5.0). Autoimmune screening was negative. However, the N-Methyl-D-Aspartic acid receptor antibody test then showed a positive result.

On day 15 of admission, she underwent a right salpingo-oophorectomy for the right ovarian teratoma. Intraoperative, the right ovarian mass was fully occupied by a smooth solid cystic tumour measuring around 10cm x 8cm and contained hair and sebum material (Fig. 1). The histopathological examination result showed ovarian immature teratoma grade 2 with the presence of immature primitive glial tissue.

Six hours postoperation, she had an episode of acute delirium with laughing and crying that resolved after 5 mg of Haloperidol. The following day, she had mild grade fever and was started on antibiotics for postoperative nosocomial infections. Despite this intervention, she developed blepharospasm and a kinetic mutism, followed by fine tremors, bradykinesia and mask-like facies. Hence, she was started on intravenous immunoglobulin 0.4 mg/kg/day for 5 days. A week later, patient became more responsive, seizures and psychosis behaviour subsided. Furthermore, hypomimia and bradykinesia have also improved. She was discharged home well with tapering dose of oral prednisolone, levetiracetam and sodium valproate.

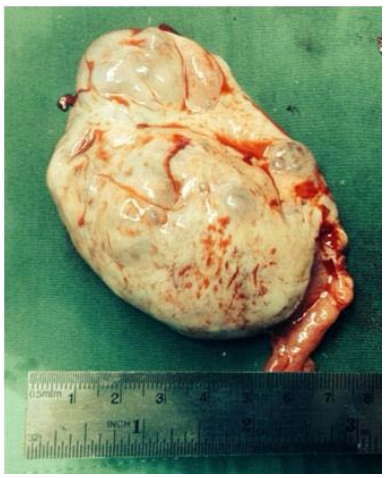

Figure 1: Right ovarian immature teratoma

She underwent four cycles of chemotherapy and remained asymptomatic with no recurrence of ovarian cyst. Neurologically she had no more seizures or dyskinesia and had recovered her cognitive function. Her steroid was tapered off after one year. Nevertheless, she had amnesia and was unable to recall the entire event. Her final complete diagnosis was paraneoplastic anti-NMDAR encephalitis secondary to immature teratoma.

Discussion

Anti-NMDAR encephalitis was first reported by Dalmau et al. (2) almost a decade ago. Following that, several reports were published where majority of cases had mature ovarian teratoma (3) unlike immature teratoma found in this case. Other tumours include small cells lung cancer (4), mediastinal tumours (1), bilateral testicular teratoma and seminoma in males (5). Lebas et al. (6) reported another interesting case of a young boy presented with anti-NMDAR encephalitis due to neuroblastoma. Anti-NMDAR encephalitis during pregnancy had been reported as well (7).

The exact pathogenesis remained unknown. Prodromal symptoms may result from part of an early immune activation or the immune response across blood-brain barrier (4). It was postulated that ectopic expression of NR2 subunit-related antibodies by the nervous tissue content with some forming rosette in the teratoma contribute to reducing immune tolerance. Hence, formation of autobodies against NMDA receptor in the brain causes paraneoplastic neurologic syndrome (8). The fact that, this patient presented with neurological symptoms, psychiatric changes and not with gynaecological symptoms had put the priority of her gynaecology problem last.

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Patients commonly present at their first and second decade of life with the mean age of 24 years old, a perfect timing for this patient (3). Clinical symptoms of anti-NMDAR encephalitis include prodromal symptoms mimicking flu and headache then followed by abnormal involuntary movements of facial muscles, seizures, cognitive problem and psychosis (1,4). Due to low suspicion of encephalitis, with the presence of ovarian tumour, majority of the cases had an extended time lapse between diagnosis and surgery. A review by Acién et al. (3) showed that the median time to surgery was 71.4 ± 88.5 days. On contrary in this current patient, she was treated for neurological and psychiatric problems first before realizing that there was a link with her ovarian mass. To date, there is no established guideline to specifically address its management.

Majority of reviews suggested early detection and removal of teratoma resulted in a better outcome (1, 3). Imaging studies such as pelvic ultrasound computed tomography and MRI are useful in screening for an ovarian teratoma. Hayashi et al. reported a 7mm ovarian teratoma was detected via MRI examination which had resulted in a successful laparoscopic resection (9). A review from Japan by Iizuka et al. (10) had reported a spontaneous recovery even without tumour removal. On contrary death had been reported due to delay in diagnosis of tumour (3, 11,12). A few reports also showed that clinical improvement with blind ovariectomy despite negative imaging which later revealed an occult teratoma (13,14,15). In this patient a right salpingo-oophorectomy was performed as the tumour was big.

Teratoma is the most common ovarian germ cell tumuor and also the most common ovarian neoplasm in patients younger than 20 years old (16). Nevertheless in a patient with teratoma without any neurological symptoms, systemic screening of anti-NMDAR antibodies is not warranted (17). A review of 100 cases of anti-NMDAR encephalitis by Dalmau et al. (4) showed that 75 % recovered or had a mild deficit while the remaining had severe deficit or passed away. In the present case, the patient remained asymptomatic without recurrence for one year, until today.

Conclusion

Association of ovarian mass with anti-NMDAR encephalitis has long been detected. Nevertheless, the association is not always obvious clinically during the working diagnosis. A clinician should consider anti-NMDAR encephalitis in a young patient presenting with encephalitis of uncertain etiology and geared towards diagnostic work up with pelvic imaging for ovarian masses to ensure timely treatment.

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