CASE REPORT

Mature ovarian teratoma associated with anti-N-Methyl-D-aspartate receptor encephalitis: A case report

I Nyoman Bayu Mahendra, PhD[1], Kade Yudi Saspriyana, MD[1], Ni Putu Ekawati, MD[2]

[1]Gynecology Oncology Division, Department of Obstetrics and Gynecology, Faculty of Medicine, Udayana University, Sanglah General Hospital Bali, Jalan Diponegoro, Denpasar, Bali, [2]Department of Pathology Anatomy, Faculty of Medicine, Udayana University, Sanglah General Hospital Bali, Jalan Diponegoro, Denpasar, Bali

SUMMARY

Encephalitis associated with anti-N-Methyl-D-aspartate (NMDA) receptor is a rare form of autoimmune encephalitis. We report the first case of anti-NMDAR encephalitis in an unmarried 16-years old female who was admitted to the Neurology Emergency Unit Faculty of Medicine, Udayana University, Sanglah General Hospital Bali, Indonesia due to decreased consciousness, repetitive talking, headache, involuntary movements in the mouth and feet, and seizures. She was initially diagnosed with viral encephalitis and symptomatic epilepsy. After four weeks of treatment, she was referred to the Gynecology Department. Rectal ultrasound revealed a cystic lesion with a solid component measuring 3.6x2.64x3.18 cm from the left ovary. Laparotomy cystectomy was performed, and the histopathological examination revealed glial cells and mesoderm components in the form of cartilage tissue. Serum and cerebrospinal fluid were positive for anti-NMDA receptor antibodies. She was treated with human intravenous immunoglobulin and rituximab. Her condition was improved gradually. She recovered fully after almost six weeks of hospitalisation.

INTRODUCTION

The ovarian mature cystic teratoma, which leads to anti-N-methyl-D-Aspartate Receptor encephalitis (NMDAR) is a rare case and often undiagnosed.[1] The first case of NMDAR encephalitis was detected in 1997 and was formally defined in 2007 by Dalmau et al.[2] Based on the systematic review by Acien et al. showed 157 cases of NMDAR throughout the world for the period 2007-2013.[3] Although rare, it is the second most common cause of immune-mediated encephalitis secondary to antibodies to the N-methyl D-aspartate receptor. It may be the cause of encephalitis in up to 4% of patients.[1]

NMDAR encephalitis is a disease that can cause severe symptoms that can lead to death. This disease causes psychiatric symptoms, seizures, memory deficits, and reduced awareness which often requires ventilator support.[2] Three risk factors that are associated are: adolescent female, the presence of ovarian teratomas, and detection of antibodies NMDAR in the serum. Since 2007, there has been a progressive increase in the number of articles and case reports. Thus, it appears that the incidence of this condition is higher than previously estimated and will continue to increase with improvements in health care, knowledge of the disease and improved socioeconomic development.[3]

Up to 77% of NMDAR encephalitis patients are initially seen by psychiatrists and misdiagnosed with new-onset schizophrenia or bipolar disorder.[3] Given approximately 60% of cases in women are caused by an ovarian teratoma, it is essential to rule out an ovarian mass when anti-NMDA encephalitis is the differential diagnoses.[1] There are differences of opinion amongst gynaecologists about the best surgical approach to manage ovarian mature cystic teratoma. There is a lack of well-designed comparative clinical trials to define the criteria to select a particular technique, and consequently, there are variations in surgical practices.[4] If untreated, the disease can lead to lethal hypoventilation, autonomic instability, and catatonia.[4]

Here we report a case of mature ovarian teratoma associated with probable anti-N-Methyl-D-aspartate receptor encephalitis. The case was successfully managed through a comprehensive multidisciplinary collaboration involving a gynaecologist, neurologist, rheumatologist, and intensive care specialist.

CASE DESCRIPTION

A 16 years old female patient was admitted to the intensive care unit (ICU) of the Sanglah Hospital, Denpasar, Bali, Indonesia, in July 2017 due to a decreased consciousness, repetitive talking, headache, involuntary movements on mouth and feet, and seizures. Physical examination upon admission revealed a decreased Glasgow Coma Scale (eye response: 2; verbal response: could not be measured; movement response: 2), blood pressure was 144/61mmHg, pulse was 84 times per minute, respiratory rate was 18 times per minute, and body temperature was 38.3°C. The neurological examination concluded cranial nerves paralysis of the 7th and 12th with complex partial seizures. CT scan and lumbar puncture showed no abnormalities. EEG performed on 1st and 7th day after seizures. The result was a deflection on left temporal and extent to other brain regions, respectively. Initial diagnosis included viral encephalitis, with differential diagnosis of autoimmune encephalitis. She was initially treated with anticonvulsants (oxcarbazepine, phenytoin), neuroprotector, vitamin B, and intravenous immunoglobulin.

After almost four weeks of treatment, as seizures persisted, a prompt diagnosis was not establish as yet. Multidisciplinary team meeting (Neurologist, Internist, Intensivist, Anesthesiologist) suspected encephalitis associated with anti-

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Corresponding Author: I Nyoman Bayu Mahendra
Email: bayu.mahendra.nyoman@gmail.com

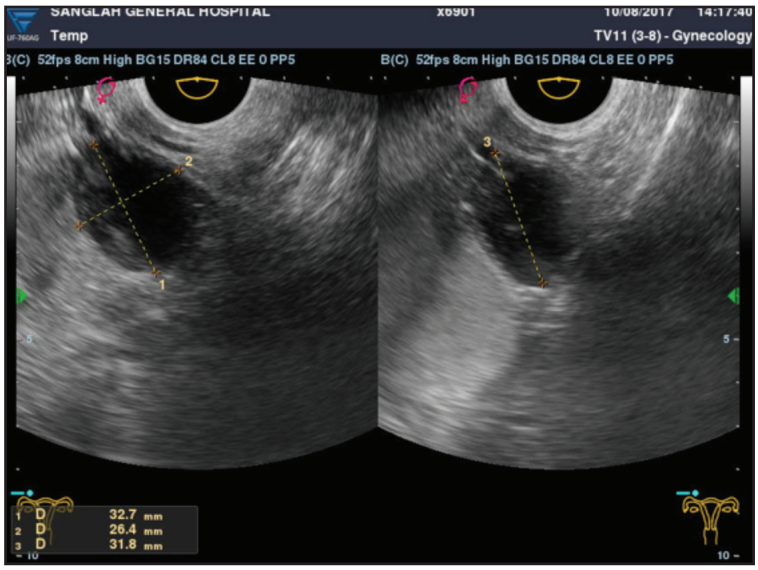

Fig. 1: The picture from rectal sonography reveals a cystic lesion from the left adnexa with 3.2x2.64 cm dimensions on the longitudinal plane (left) and 3.18 cm dimension on the transversal plane (right). US performed using GE Logiq V5.

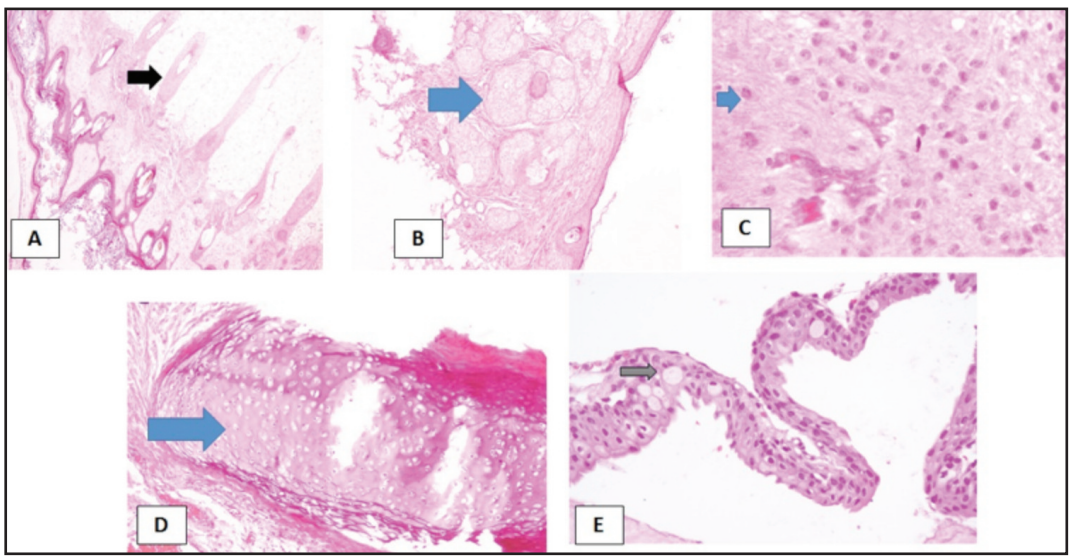

Fig. 2: A panel of histological examination from the cystic mass showing hallmarks of ectoderm: hair follicle (A), sebaceous gland (B), a glial component of the tumour (C); mesoderm layer: cartilage (D); and endoderm layer: cuboid epithelial with goblet cell (E). (Hematoxylin Eosin staining, magnification 100x, light microscopy).

NMDA receptor and suggested an abdominal ultrasound to rule out abnormality in the abdominal cavity. The abdominal ultrasound (US) revealed a cystic mass with solid component in left adnexa size 3x3 cm. Then, the patient consulted with the Gynecology Department. In the abdominal ultrasound, a left adnexal cystic lesion with solid components in size of 3.6x3.2 cm was found. Rectal ultrasound revealed ovarian cysts of 3.2 x 2.64 x 3.18 cm dimension. The diagnosis was a functional cyst, while the differential diagnosis was a dermoid cyst. The picture of rectal sonography image is presented in Figure 1. Laparotomy left cystectomy was performed and found a 4x2x2 cm cysts.

Histopathology examination observed under a light microscope after haematoxylin and eosin staining revealed yst walls containing ovarian connective tissue, corpus albican and follicular cysts. The cyst tissue contains ectoderm components, i.e., squamous epithelium and their adnexa (sebaceous glands, hair follicles), glial cells and mesoderm components in the form of cartilage tissue. It was concluded that the histomorphology appearance was indicative of mature cystic teratomas (Figure 2).

Testing for NMDAR antibodies was unavailable at Sanglah Hospital Bali. We sent the blood, and cerebrospinal fluid of the patient for the NMDAR antibodies to be tested in Clinical Pathology Clinic Cipto Mangunkusumo Hospital/Faculty of Medicine Universitas Indonesia, Jakarta. The results of anti-NMDAR antibodies in both the serum and CSF of patients was positive.

After the surgery, first-line medical therapy included steroid, intravenous immunoglobulin (IVIG), plasmapheresis and rituximab. The steroid used as antiinflammation and immunosuppressive to prevent CNS damage. The rationale used of IVIG to decrease T-cell proliferation and cytokine level and depresses B-cell differentiation. The benefit of plasmapheresis was removed antibodies and inflammation mediator, such us serum cytokine. Rituximab function, in this case, diminished the CNS antibodies, including B-cell. After the complete treatment, condition of the patient improved. She was sent home from the hospital with good consciousness. However, her speech was slurred; continued using a urine hose and walked with an ataxic gait. Speech and physical walking physiotherapy were continued regularly for six months. At the end of the treatment, the patient could speak fluently and resumed school again.

DISCUSSION

Mature cystic teratomas are ovarian neoplasm which contain mature tissue components originating from two or three germinal layers.[4] These tumours are more often cystic, rarely solid. Macroscopically this can be a unilocular cyst that contains sebaceous material and hair, and sometimes there are teeth. Microscopically, the ectoderm component can be squamous epithelial cells, the structure of adnexa, and brain tissue (glia, ependymal tubule, and cerebellum). The mesoderm component can be bone, cartilage, smooth muscle, and adipose tissue. The endoderm components can be gastrointestinal, respiratory or bronchial epithelium, thyroid, and salivary gland.[5,6]

The ovarian cystic mature teratoma can lead to anti-N-methyl-D-Aspartate Receptor encephalitis (NMDAR). It is hypothesised that the glial cells present within the teratoma produce antibodies to NMDAR, which in turn cause severe encephalitis. The cause of that antibody production is still unknown. The targets are NR 1 and NR 2 subunits at NMDA receptors, which cause reduced synaptic plasticity. This change reduces NMDAR activity, which affects cognitive and behavioural deficits leading to schizophrenia and psychosis. With the removal of this teratoma, it will stop the production of the antibody.[7]

Anti-NMDAR encephalitis caused by mature cystic ovary teratoma is a difficult disease to diagnose. Histological and antibodies examination is needed to confirm the diagnosis. In our case, the histology of cystic teratomas was observed. The management of the case requires interdisciplinary collaboration, (gynaecology, neurology, rheumatology, and intensive care) in order to establish careful management including early diagnosis, standard operative procedures, selection of therapies, follow-up, suppressive immunotherapy and evaluation of recurrence.[5,8] The prognosis depends on the early diagnosis and appropriate treatment given. Our case is interesting because the incidence of this disease is infrequent, and there is no consensus on strategy and management.

Tumour removal and immuno-therapy (immunoglobulin, corticosteroids, plasmapheresis and rituximab) were performed in this case. Both procedures must be done to get the right and fast recovery. Before the tumour was removed, the psychomotor and hemodynamic condition of the patient must be stable. If the tumour is not remove early, it can result in death.[1] Intravenous immunoglobulin and plasmapheresis are very useful, but the treatment often fails if there is the involvement of the central nervous system. A positive response to plasmapheresis supports the argument that this disease is due to increased antibodies.[9] Seizures associated with anti-NMDAR encephalitis are often challenging to treat with antiepileptic drugs. Abnormal EEGs are usually found despite antiepileptic therapy at maximum doses. Immunotherapy such as IVIG is useful in dealing with seizures that do not respond to antiepilepsy.[9]

Prognosis varies considerably based on the time of diagnosis, neurological diagnosis, identification and removal of the tumour.[7,10] However, we are still investigating about the prognosis of our case. This case is rare and difficult to treat. We need clear protocols for the management of the disease. Until now, no report has stated that the prognosis is good. This case was the first case of encephalitis associated with anti NMDAR caused by ovarian cystic mature teratoma in Sanglah General Hospital, Bali, Indonesia.

Our experience in managing this case has resulted in the following producing some recommendations, regarding possibility misdiagnosis as psychiatric disease or other types of encephalitis. We emphasise the importance of multidisciplinary collaboration to make a diagnosis as soon as possible in this particular disease. Treatment strategy in case of the ovarian tumour as suspected aetiology, surgery followed by immunotherapy will result in maximal outcome for the patient. A comprehensive approach, continuing monitoring must be performed every 3-6 months for the first five years after completing the therapy. All these strategies will avoid permanent damage and disability to the patient.

CONCLUSION

Ovarian mature cystic teratoma, which leads to anti-N-methyl-D-Aspartate Receptor encephalitis (NMDAR) is a sporadic case and often challenging to diagnose. In the present case, the small size of the tumour made diagnosis difficult, causing a delay in the final diagnosis. However, there has been a substantial improvement six months after the surgery. Management of the case required experts in gynaecology, neurology, rheumatology, and intensive care to establish careful management that included early diagnosis, standard operative procedures, selection of therapies, follow-up, suppressive immunotherapy, and evaluation of recurrence. This positive response to surgery and immunosuppressant therapy underlines the fact that early diagnosis is of paramount importance, as it may result in almost complete recovery. There is a need for further multicenter studies to investigate the prognosis of anti NMDAR encephalitis.

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