Ovarian teratoma-associated anti-NMDAR encephalitis in a 12-year-old girl

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SUMMARY

The association of ovarian teratoma and anti-N-Methyl-D-aspartate receptor (anti-NMDAR) is one of the most common autoimmune encephalitis syndromes and it is a serious and potentially fatal pathology that occurs in young women. This case report describes of a pediatric patient with anti-NMDAR encephalitis. A-12-year-old girl presented with abnormal behavior for one week came to Emergency Department of Sarawak General Hospital, Malaysia. She had psychotic spectrum symptoms including suicidal tendency. She was diagnosed with anti-NMDAR encephalitis as positive antibody was seen in her cerebrospinal fluid. She was treated with Injection Immunoglobulin. She turned out to have teratoma which was successfully removed later. Her progress was remarkable after the surgery with the Immunoglobulin. A multi-disciplinary team involving a psychiatrist, neurologist and gynaecologist liaised with intensivist to successfully manage the case and achieve the good outcome.

INTRODUCTION

The association between ovarian teratoma and anti-N-Methyl-D-aspartate receptor (Anti-NMDAR) is now recognized by most of clinicians. In a cohort study of Titulaer MJ et al.[4] with 577 anti-NMDAR encephalitis patients had observed that Asian and African-American patients found out that large group of the patients 220 (38%) had teratoma, especially in women 213(46%). Anti-NMDAR cases were rarely seen in girls of age younger than 12 years is only 4 (6%) and male patients 7(6%) in that study. This case report a serious and potentially fatal pathology named autoimmune encephalitis syndrome in a 12-year-old previously healthy girl. In this case, we successfully managed the anti-NMDAR encephalitis with previous unknown history of teratoma in a young girl by a competent multi-disciplinary management in order to share this uncommon pathology with other clinicians.

CASE REPORT

A 12-year-old girl who presented with a sudden development of abnormal behavior for one week came to the Emergency Department of Sarawak General Hospital. She was treated for some psychiatric problems in a private hospital last a few days ago. She had no medical illness before this incidence with no family history of psychiatric illness. History of illicit drug use and travel history were ruled out.

On examination, the patient was afebrile and her vital signs were normal and stable. Her Glasgow Coma Score was 13/15 on that time. All systemic examinations were unremarkable. All routine necessary blood tests were done and results were within normal limit. She was seen by psychiatric team to rule out psychosis and other psychiatric disorders while waiting for advanced investigations. Computerized tomographic brain scan was done and the result revealed there was no gross abnormality. Magnetic Resonance Imaging reported absence of space occupying lesion or any demyelinating lesions were detected. However, Electroencephalogram (EEG) result indicated an abnormal EEG with continuous delta wave suggestive of severe encephalopathy. She developed nystagmus movement for 10-20 seconds which was suspected to be a seizure while in the emergency department and she was given intravenous phenytoin to control her seizure. Her condition worsened as she lost consciousness after admission. We proceeded to lumbar puncture (LP) the next day. There have differential diagnoses like schizophrenia, substance abuse or malingering, the vigilant expertise of our neurological team, they looked for anti-NMDAR antibodies in the cerebrospinal fluid of the patient. LP result confirmed the presence of anti-NMDAR antibodies (positive) with plasma glucose of 0.6 and 1.4 in lymphocytes count. Again, the neurologist took care of the patient referred her to the Obstetrics and Gynaecology team in order to rule out ovarian tumour especially teratoma. Transabdominal ultrasound was done and there was a well-defined solid cystic lesion 5.5x5x4.7cm at vesico-uterine pouch with hyperechoic nodule and calcification. Tumour marker was taken and all were within normal limits.

Laparotomy with left ovarian cystectomy was performed and the sample was sent for histopathological examination (HPE), together with minimal peritoneal fluid for cytological examination. Both her fallopian tubes, the right ovary and uterus were normal. She was treated with intravenous (IV) immunoglobulin and IV methylprednisolone for 5 days followed by oral prednisolone tablets. Fig (1) showed HPE microscopic appearance. The microscopic feature shows that cyst wall is partly lined by keratinized stratified squamous (f)

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Table I: Yellow flag symptoms and Red flag symptoms

Yellow Flag	Red Flag
- Decreased level of consciousness	• CSF – Pleocytosis
- Abnormal postures/movements	- Oligoclonal bands without infection
- Autonomic instability	- Elevated or normal protein
- Focal neurological deficits	- Normal Glucose
- Aphasia/Dysarthria	• Generalized seizure
- Rapid progression of psychosis despite therapy	• Faciobrachial seizures
- Hyponatraemia	• Suspected neuroleptic malignant syndrome (NMS)
- Catatonia	• MRI abnormalities (Mesiotemporal hyperintensities, atrophy pattern)
- Headache	• EEG abnormalities (slowing, epileptic activity or extreme delta brush)

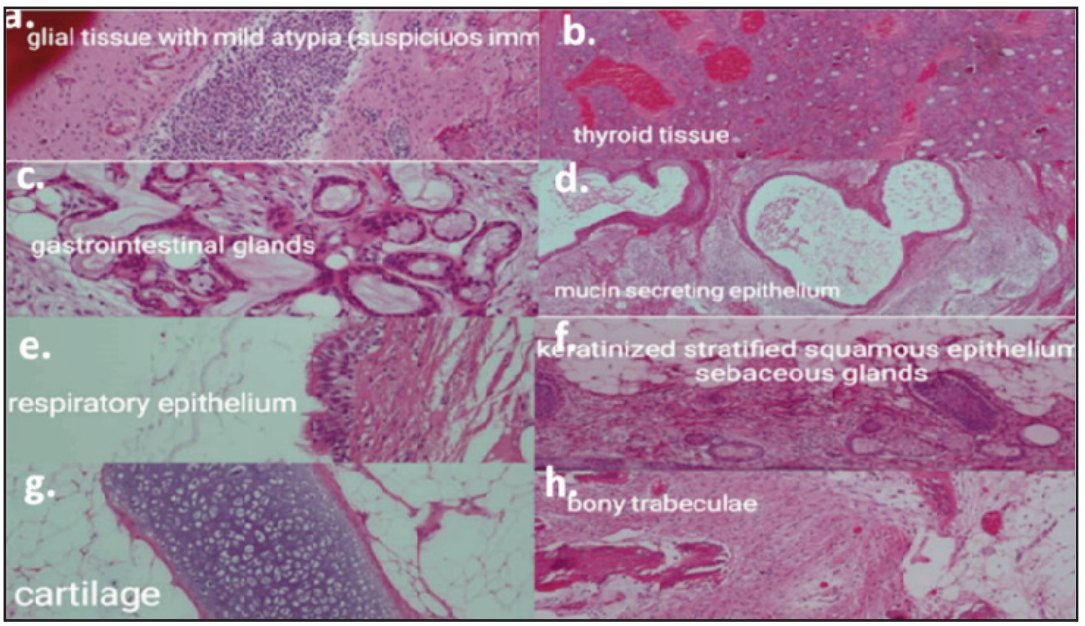

Fig. 1: Histopathological examination showing the microscopic features.

and some respiratory epithelium (e). The underlying cyst wall shows and sebaceous glands (f), glial tissues and nerve bundles (a). Mesodermal derivatives consisting of bone (h), cartilage (g), fatty tissue gastero-intestinal glands and thyroid glands (b, c and d) and no evidence of malignancy.

She was admitted to the Intensive Care Unit (ICU) for 2 days after operation and once stable, was transferred to medical ward. She had one episode of seizure in each day of 3rd and 4th post-operative day. The fits were aborted by Injection Diazepam stat dose. She was restless and she could move her limbs on 4th and 5th post-operative day. She was able to obey the commands of the medical staffs, tolerate nasogastric tube feeding on 6th post-operative day. She was able to communicate again with her family members and her sleep pattern returned to normal after 9 days of operation. After that, she recovered gradually. There were no more fitting episodes and abnormal behaviour. She was discharged 23 days after operation. She was well and healthy at the time of follow-up one month after discharge from hospital.

DISCUSSION

There are increasing in the speculations of the role of autoimmune antibodies playing an important role in mental disorders. In case of autoimmune encephalitis, N-Methyl –D-Aspartate receptor antibody was assumed to be a causation of psychotic symptoms.

Herkin and Pruss[2] proposed "yellow flag" symptoms (i.e. raising suspicion) which indicates an autoimmune process and "red flag" symptoms pointing out the potential antibody involvement.

Early recognition of these symptoms will help clinicians to get an early diagnosis, implementation of effective treatment resulting in good achievement in patient's outcome.

Anti-NMDA receptor encephalitis is an autoimmune disease caused by own antibodies attacking against the NMDA receptor 1 (NR1) subunit of the NMDA receptor in the brain. NMDA receptors are proteins that control electrical impulses in the brain. Therefore, the normal brain signal is disrupted and it will affect the human memory, cognition and learning ability. The affected area is the limbic system. Primarily in the frontotemporal and hippocampal region. It can affect both men and women, however, is more common among women. In men, it can be associated with testicular teratoma. It primarily affects the young, including children and young adults mainly >18 years and above.[3] Some patients also have

a tumour associated with this disease; the most common type is an ovarian teratoma in women like in our case. The exact incidence of the disease is unknown.

Clinical Presentations

There are case reports especially in psychiatric literature reporting the significant overlap between the neurologic and psychiatric pathology associated with autoimmune encephalitis.[1] It is followed by psychotic phase in which the symptoms of delusions, hallucinations and paranoia. Memory loss, failed concentration with disorganization in both thought process and behavior may occur. Therefore, this case could be mistaken with schizophrenia, substance abuse or malingering. However, as the disease worsens, the autonomic dysfunction like hypertension, hyperthermia, tachycardia, hypoventilation sets in. Then, the seizures, and movement disorders appear. Catatonia may develop, but speech and verbal abilities decline.

Diagnosis

Anti-NMDAR antibodies in the cerebrospinal fluid (CSF) is the main diagnostic test but serum assays are not as sensitive as those from CSF. CSF reveals pleocytosis, oligoclonal bands without infection, elevated or normal protein and normal glucose. Brain magnetic resonance imaging (MRI) has been reported to be negative in up to 50-70% of cases. EEG may show abnormal slowing but is nonspecific in 90% of patients. One study concluded that the sensitivity of Brain MRI, EEG and CSF were 33%, 90% and 79% of patients respectively.[5] In our case report, EEG suggested of severe encephalitis with the continuous delta wave and positive anti-NMDAR antibodies in CSF. The expert opinion in the literature recommends clinicians to screen for teratoma or germ cell tumours as in our case.

Treatment

The following treatment is recommended from most studies. First line treatment is the removal of tumour, if tumour is present, giving steroids, intravenous immunoglobulin and plasmapheresis. Second line of treatment is giving CellCept, rituximab and Cytoxan. Tumour removal will lead to improvement of the patient neurological performance within days or weeks. In our case, patient regained her conscious level within one week.

CONCLUSION

The disease entity itself is complicated and overlapping with a psychiatric spectrum. Therefore, collaboration between multi-disciplinary team provides the timely intervention and furbish the steps in requesting the necessary investigation like MRI/EEG and CSF variables to achieve the correct diagnosis. All health personals should equip themselves with up to date knowledge and information from the literature and pertinent facts while considering the diagnosis and effective treatment in dealing with uncommon and unusual cases like ours.

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CONSENT

Written informed consent was obtained from the patient's mother for publication of this case report and all accompanying images.

CONFLICTS OF INTEREST

The authors declare that there was no potential conflict of interest relevant to this article was reported.

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