Case report

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Occult teratoma in a case of N-methyl-D-aspartate receptor encephalitis

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Abstract

N-methyl-D-aspartate receptor encephalitis (NMDARe) is one of 13 autoimmune-mediated encephalitides that have been discovered over the last decade. This case report describes the course of a 26-year-old female who presented with new-onset seizures and insomnia, complicated by encephalitis. The initial workup ruled out common causes of encephalitis, while a transvaginal ultrasound (TVUS), and computed tomography (CT) scans of the chest, abdomen, and pelvis did not identify a mass. Based on the suspicion that she may have autoimmune encephalitis, the patient was treated with intravenous immunoglobulins and plasma exchange, but continued to deteriorate. Whole-body positron emission tomography (PET) scan identified a small hypermetabolic pelvic mass. Shortly thereafter serum and cerebral spinal fluid NMDAR antibody titers were reported as positive, prompting repetition of the TVUS, which confirmed the presence of an ovarian teratoma. The patient had a laparoscopic oophorectomy with subsequent resolution of her symptoms, further confirming the diagnosis. Despite the sensitivities of TVUS and CT of up to 94% and 98%, respectively, the teratoma was unusually small, necessitating the addition of a PET scan to identify the lesion. These neoplasms are thought to have low uptake on PET; however, it is possible that focal inflammation may have enhanced the detection. It is unlikely that the teratoma grew during hospitalization as the average growth rate is 1.8 mm per year. Regardless, the lesson that can be learned is that imaging modalities beyond CT and TVUS, such as PET, can be helpful, as identification of a resectable tumor may alter management and ultimately improve outcomes.

Keywords

Seizures, psychosis, encephalitis, NMDA receptor, teratoma, PET

Introduction

Since the description of N-methyl-D-aspartate receptor encephalitis (NMDARe) as an entity in 2007, 12 other autoimmune-mediated encephalitides have been discovered.[1,2] NMDARe is more common than previously thought; a study performed by Granerod et al. reported that NMDARe is the second leading cause of autoimmune-mediated encephalitis.[3] Clinical features include fever, headaches, nausea, restlessness, diarrhea, central hypoventilation, oral facial dyskinesia, affective disturbance, psychosis, hallucinations, memory loss, seizures, dyskinesias, vegetative deregulation, and autonomic dysfunction.[1,4–6] Neuropsychiatric disturbance and seizures can help distinguish NMDARe from other autoimmune encephalitides.[4]

NMDARe is more common in women who are in their second to fifth decades of life.[1,2,4] It has been associated with sex-cord stromal tumors, immature teratomas of the testis, neuroendocrine tumors, mediastinal tumors, neuroblastoma, Hodgkin's lymphoma, and breast cancer.[1,5] The pathophysiology of NMDARe is not well understood.[7,8] In cases in which the patient has a teratoma, it is thought that the tumor triggers production of antibodies against the NR1 and/or NR2 subunits of the N-methyl-D-aspartate subtype glutamate receptor (NMDAR).[6] When a tumor is absent, other immunological mechanisms and genetic predisposition likely play a role.[7,8]

NMDARe is diagnosed by detection of immunoglobulin G antibodies against the glutamate NR1 or

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NR2 subunits of the NMDAR in the serum and/or with a higher sensitivity in the cerebral spinal fluid (CSF).[1] Electroencephalogram (EEG) may demonstrate nonspecific focal slowing, epileptiform activity, and periodic lateralization epileptiform discharges that can be used to exclude non-convulsive seizures.[9] Fifty percent to 90% of patients with NMDARe will have normal brain magnetic resonance imaging (MRI) scans, while other patients typically exhibit T2/fluid-attenuated inversion recovery signal hyperintensities extending beyond the limbic system.[2,9,10] Fluorodeoxyglucose positron emission tomography (FDG-PET) may reveal scattered cerebral hyper- and hypometabolic foci commonly without MRI correlate.[11] An associated neoplasm may be detected by whole-body computed tomography (CT) and MRI scans, in conjunction with ultrasound studies. Whole-body PET may have added value in identifying neoplasms especially in the setting of negative screening with other imaging studies that are limited by lower specificity.[9,11]

Acutely NMDARe is managed with corticosteroids, intravenous immunoglobulins (IVIg), plasma exchange, and tumor resection if one is identified.[6] Once the acute phase has resolved, the patient may receive rituximab, cyclophosphamide, mycophenolate mofetil or azathioprine to prevent a reoccurrence, which occurs in 12% to 24% of cases.[1,4,6,9,12]

Case presentation

A 26-year-old female presented to the hospital for evaluation of new-onset seizures leading to a motor vehicle accident. She had no past medical history, medications, allergies, contributing family medical history, or significant social history. After evaluation, she was discharged from the hospital, but continued to have seizures. Upon readmission she was started on levetiracetam and diazepam, and then discharged home. Over the next few days she had staring spells, auditory hallucinations, and insomnia. She was subsequently re-admitted for additional testing.

Her complete blood count, serum chemistries, liver function tests, urine toxicology screen, chest x-ray, and EEG were unremarkable. A lumbar puncture was performed, but the tap was traumatic, therefore it was difficult to interpret the cell count and differential (Table 1). The rest of the CSF analysis was negative for Venereal Disease Research Laboratory (VDRL), Herpes Simplex Virus (HSV) I and II, cryptococcal antigen, West Nile virus, and Lyme's disease. MRI of the brain showed subtle engorgement of the right temporal lobe and cortical gyri, without T2 signal or diffusion restriction (Figure 1(a)). Serum antinuclear antibodies (Ab), erythrocyte sedimentation rate, C-reactive protein, carcinoembryonic antigen, alpha feto-protein, beta human chorionic gonadotropin,

Table 1. LP results.

	First LP	Second LP	Normal
Color	Red	Red	Colorless
Clarity	Cloudy	Cloudy	Clear
CSF WBC	135 cells/ul	24 cells/ul	0–5 cells/ul
CSF RBC	114,000 RBC/mm^3	64,500 RBC/mm^3	0–10 RBC/mm^3
CSF neutrophils	5%	36%	0–6%
CSF lymphocytes	94%	64%	40–80%
CSF monocytes	1%	0%	15–45%
CSF histiocytes	0%	0%	0%
Xanthochromia	Present	Present	None
CSF glucose	–	50 mg/dl	45–80 mg/dl
CSF protein	–	256 mg/dl	15–45 mg/dl
CSF culture	Negative	Negative	Negative
CSF IgG	–	45.7 mg/dl	0.0–6.0 mg/dl
CSF albumin	–	139 mg/dl	0.0–35 mg/dl
Serum albumin	–	3820 mg/dl	3500–5200 mg/dl
Albumin index	–	36.4	0–9 (ratio)
IgG index	–	0.84	0.28–0.66 (ratio)
CSF IgG/albumin ratio	–	0.33	0.09–0.25 (ratio)
CSF oligoclonal Bands	–	Negative	Negative
CSF synthesis rate	–	105.0 mg/24 hours	0–8 mg/24 hours
Band number	–	0	0
CSF ACE	–	1.9 U/l	0–2.5 U/l

ACE: angiotensin-converting enzyme; CSF: cerebral spinal fluid; IgG: immunoglobulin G; LP: lumbar puncture; RBC: red blood cells; WBC: white blood cells.

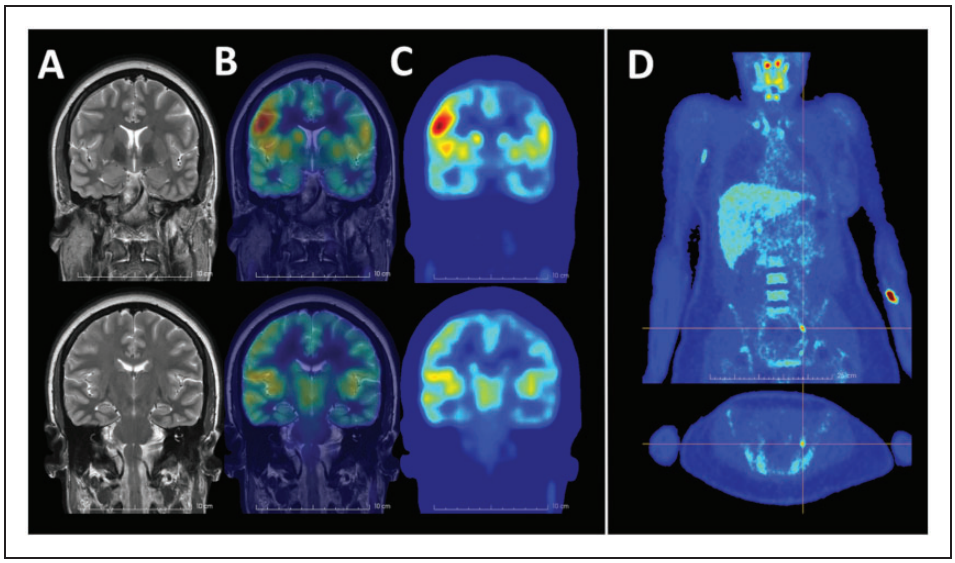

Figure 1. Coronal T2-weighted MRI (a) of the patient showing subtle cortical thickening in the right hemisphere most prominently in the temporal lobe. T2-weighted MRI images superimposed with FDG-PET (b) and source FDG-PET (c) images showing right frontal hypermetabolism with asymmetric metabolic activities in the temporal lobes and hypometabolism without obvious MRI correlate. Coronal and axial views of whole-body PET scan (d) revealing a small hypermetabolic left ovarian mass consistent with the teratoma. MRI: magnetic resonance imaging; FDG-PET: fluorodeoxyglucose positron emission tomography.

thyroid peroxidase Ab, anti-thyroglobulin Ab, lactate dehydrogenase, cancer antigen (CA) 125, CA 19-9, neuronal nuclear Ab (Anna-1, Anna-2, Anna-3), neuronal and muscle cytoplasmic Ab (PCA 1, PCA 2, PCA Tr, amphiphysin, CRMP-5, striational), plasma membrane cation channel Ab, calcium (Ca) channel Ab, P/Q type Ab, N Type Ca channel Ab, acetylcholine receptor (AChR) binding Ab, AChR ganglionic Ab, antiglial nuclear Ab Type 1, and voltage-gated potassium channel Ab were unremarkable. A CT scan of the chest, abdomen and pelvis, and transvaginal ultrasound (TVUS) did not identify a mass.

Over the next few days the patient became obtunded and had episodes of unresponsiveness while displaying various often stereotypic postures, ranging from four-limb extension, episodic fencing posturing of the upper limbs, variable degrees of lower extremity clonus to flaccidity, and episodes of waxy catatonia. With a growing suspicion for autoimmune limbic encephalitis, she was treated with a five-day course of methylprednisolone and IVIg. Despite treatment, she developed arrhythmias, hypoxia secondary to hypopnea, and was briefly intubated. Her hospital course was further complicated by generalized tonic clonic seizures necessitating aggressive antiepileptic therapy; at the time repeat EEG demonstrated intermittent generalized slowing with new intermittent rhythmic theta waves in the right temporal region.

A FDG-PET scan of her brain and whole body was performed. The brain PET showed a heterogeneous cerebral pattern of metabolism compatible with history of encephalitis (Figure 1(c)), with hypermetabolism at the right temporal lobe corresponding to the engorgement seen on the prior brain MRI (Figure 1(b)). PET imaging of the rest of her body identified a small left pelvic FDG-avid lesion (Figure 1(d)), suspected to be an ovarian mass.

Twenty-eight days later the patient's serum and CSF NMDAR Ab results returned, with titers of 1:20 and 1:10, respectively. The lumbar puncture was repeated but all the test results were negative. The patient was treated with plasma exchange and methylprednisolone for an additional five days. Thirty-one days later she had a second TVUS, which identified a hyperechoic left ovarian mass corresponding to the pelvic mass seen on PET imaging; subsequently a left salpingo-oophorectomy and peritoneal biopsy was performed. Pathology results (Figure 2) confirmed the presence of a 0.8 cm mature cystic ovarian teratoma. Thirty-five days later the patient was noted to have stabilized, but continued to have negative and positive activation signs of catatonia.

After 42 days she was transferred to a rehabilitation facility, and then discharged home with mycophenolate mofetil, prednisone, valproic acid, and lacosamide. Forty-four days later, during a visit with her primary care provider, the patient was noted to be back to her baseline.

Discussion

During hospitalization, the patient's brain MRI showed subtle changes in the right temporal lobe and cortical gyri that corresponded to areas of increased uptake on PET imaging. The brain PET confirmed the diagnosis of limbic encephalitis before the NMDAR Ab test results returned, while whole-body PET identified a small pelvic mass that was undetected on the first TVUS and CT of the pelvis. These findings prompted acquisition of a second TVUS. It

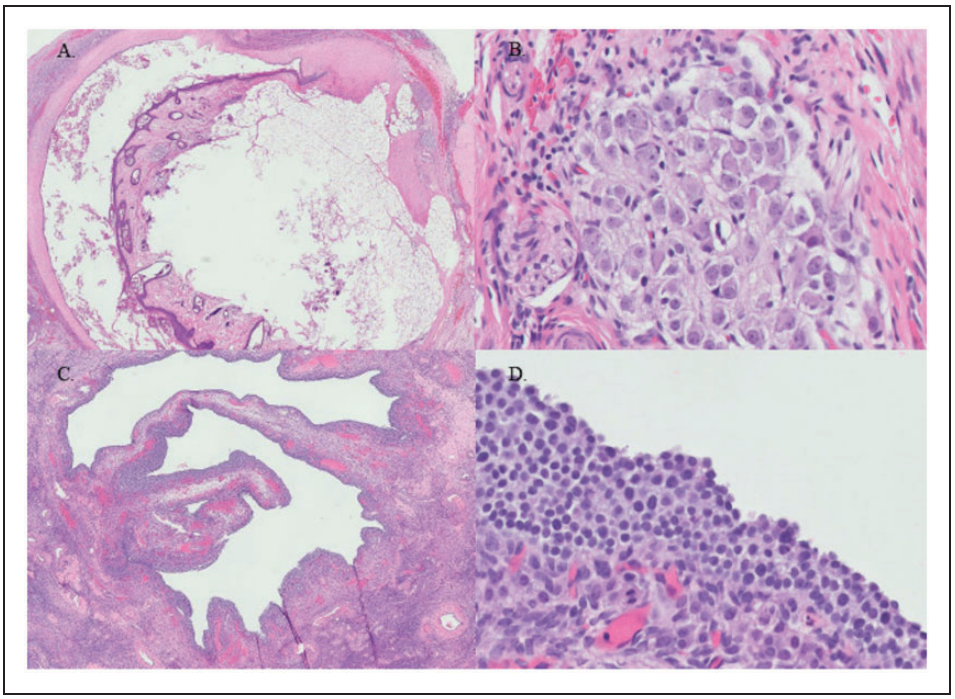

Figure 2. Section of mature teratoma showing (a) predominance of skin and mature adipose tissue (hematoxylin and eosin (H&E), 1×), and (b) ganglion cells without immature neural elements in the teratoma (H&E, 40×). Ovary with (c) numerous cystic follicles (H&E, 1×). Cystic follicles (d) with a typical layer of granulosa cells and an outer layer of theca interna cells (H&E, 40×).

is important to note that the sensitivities of TVUS and CT are up to 94% and 98% respectively for teratomas.[13] Further the diameter of the present tumor, which was 0.8 cm and almost one-tenth the size of the average mature teratoma,[13] was near the resolution limit of these modalities. Fortunately, the teratoma was identified on PET imaging despite low FDG uptake. Though related clinical data are very limited, it is possible that inflammation within the teratoma, which has been described in the presence of NMDAR Ab, may have enhanced the detection by increasing FDG uptake focally.[8]

This patient's first serum and CSF antibody titers were positive. After treatment with IVIg repeat CSF titers were negative, but she continued to have symptoms. Failure to respond to IVIg may indicate the presence of an occult immunogenic tumor,[5] as was the case in this patient and prompted PET imaging. Although there was a 12-day delay in acquiring the PET scan after the CT and TVUS, the typical growth rate of a teratoma of 1.8 mm per year[14] renders detection because of acute enlargement unlikely. Regardless, the lesson that can be learned is that there may be value in performing PET scans, MRIs, as well as repeating imaging studies, because finding a resectable mass in a patient who is unresponsive to medical therapy can prevent a prolonged course and ultimately improve outcomes.[6]

Conclusion

NMDARe is a common cause of autoimmune-mediated encephalitis; therefore, clinicians should be aware of its presentation, diagnosis, and management. Ovarian teratomas associated with NMDARe may be missed on initial imaging studies, especially if they are small. A patient's failure to respond to medical therapy should prompt the clinician to aggressively search for the presence of an occult immunogenic tumor, as identification of a resectable mass may change the course of treatment and improve outcomes. Multiple imaging modalities may be required to identify an underlying neoplasm. Specifically, PET scans may help diagnose both limbic encephalitis and an associated neoplasm as well.

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Conflict of interest

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