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Case Reports

Paraneoplastic Encephalitis Presenting as Postpartum Psychosis

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Anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis is a newly described paraneoplastic limbic encephalitis syndrome characterized by the presence of antibodies directed against the NR1 subunit of the synaptic NMDA receptors, affecting young, healthy individuals, mainly women.[1] Diagnosis involves detection of anti-NMDA receptor antibodies. Over 75% of these patients initially present to psychiatric practitioners with nonspecific symptoms of anxiety, delusions, and paranoia.[1] We report a case of anti-NMDA receptor encephalitis presenting as postpartum psychosis.

Case Reports

Ms. A, a 29-year-old primiparous woman presented to the hospital at 11 weeks postpartum complaining of 2 to 3 weeks of decreased sleep and increased difficulty caring for her newborn. She had given birth to a healthy baby boy via vaginal delivery. She described memory difficulties, sensations of "déjà vu," and mild headaches. Personal medical and psychiatric history was unremarkable, she used no medication, and she denied illicit substance use. Family history was positive for depression and bipolar affective disorder.

On examination, Ms. A appeared anxious and repetitively questioned "Why did I lose my memory?" or "Haven't you asked me this before?" Vital signs were normal, she was alert and oriented, but was unable to recall three words. General and neurologic examinations were non-focal. Complete blood count, electrolytes, renal functions, and a CT scan of the head without contrast were normal. Due to increasing anxiety and delusions that her baby was dying, she was diagnosed with postpartum psychosis and admitted to the psychiatry unit. She was started on low-dose olanzapine. Adjunctive electroconvulsive therapy (ECT) was added for catatonia and a rapid progression of paranoid delusions involving the death of her newborn. On day 3 after the first ECT treatment, she developed generalized tonic-clonic seizures requiring intubation and sedation. Re-examination demonstrated continuous chewing movements around the endotracheal tube, athetotic movements of the hands, and occasional ocular bobbing (involuntary, rapid, conjugate downward movements of the eyes with a slow return to the primary position).[2]

Acyclovir and broad-spectrum antibiotics were begun. Cerebrospinal fluid (CSF) analysis revealed 46 white blood cells (predominantly lymphocytes), 0.42g/L protein, and 4.7 mmol/L glucose. Bacterial and viral cultures, cryptococcal antigen, acid-fast bacilli, herpes simplex virus and enterovirus polymerase chain reaction were negative. Brain MRI showed three nonspecific, non-gadolinium-enhancing T2 and fluid-attenuated inversion recovery hyperintensities measuring less than one centimeter in size: one adjacent to the occipital horn of the left lateral ventricle, one in the right cerebellum, and one in the left cerebellum. There was no involvement of the temporal lobes. Magnetic resonance venography (MRV) did not reveal venous sinus thrombosis. Serology revealed an elevated ESR and CRP (42 and 178.3, respectively) and minimal increased CK (259). Thyroid functions, anti-TPO antibodies, ANA, P-ANCA, C-ANCA, cryoglobulin, and rheumatoid factor were negative or normal. EEGs showed polymorphic theta rhythms with

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superimposed, generalized sharp waves occurring every 2 to 4 seconds. The sharp waves were often followed by brief, generalized 20 Hz activity that was not suppressed with the use of neuromuscular blocking agents. Orofacial dyskinesias and choreic movements of all extremities continued. The movements were complex, involving clasping of hands with interdigitation of her fingers or simultaneous extension of both arms, but they were not associated with electrographic epileptic activity and they persisted despite propofol and pancuronium. Central hypoventilation required continued intubation.

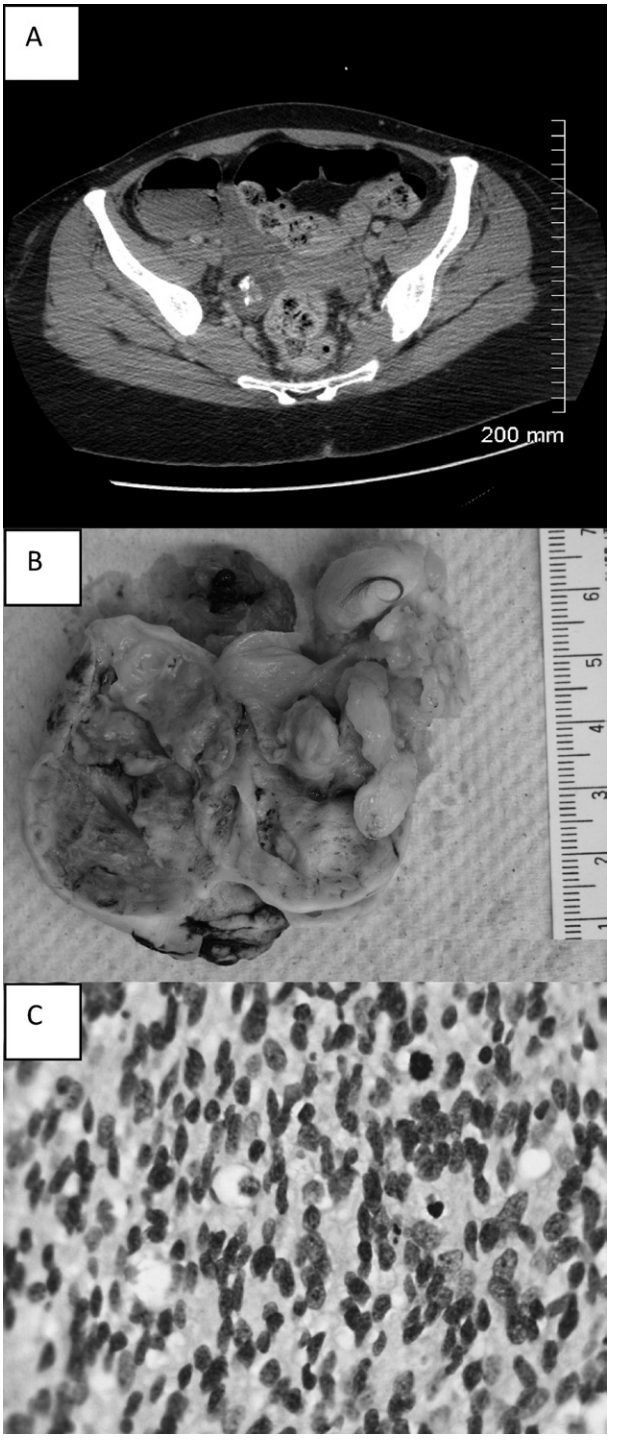
Given the clinical evolution, an abdominal CT was performed specifically searching for a neoplasm and it revealed a right ovarian mass. Prompt surgical resection confirmed a well-encapsulated grade II/III immature teratoma (Figure 1). Serum and CSF were positive for NMDA receptor antibodies.

Ms. A received methylprednisolone and plasmapheresis with little improvement. Rituximab was initiated 2 months after initial presentation. Within days, she showed dramatic improvement of the abnormal movements, tracked with her eyes, and obeyed 1-step commands. She tolerated extubation within 2 weeks of the first dose of rituximab. Repeat brain MRI 3 months after the onset of symptoms showed resolution of the nonspecific cerebellar lesions and a faint residual hyperintense signal near the left lateral ventricle. She received 2 months of rehabilitation and returned home, 8 months after the onset of her symptoms. When last seen one month later, there had been no recurrent seizures, and only minimal abnormal movements were present. Neuropsychology testing showed poor short-term memory, but preserved autobiographical retrograde memory.

Discussion

This is the first description of anti-NMDA receptor encephalitis presenting in the postpartum period. This particular period is a very unique time for the woman in terms of neuroendocrine alterations, psychosocial adjustments, sleep cycle modifications, and increased risk of certain medical conditions, including infectious processes, thrombotic events, autoimmune disorders, or vascular catastrophes to name a few.[3] The incidence of non-psychiatric causes of puerperal psychosis, such as infections, eclampsia, and cerebral venous thrombosis has decreased with improved obstetrical care. [3,4] This case demonstrates the importance of continued vigi-

FIGURE 1. **Radiologic and pathologic appearance of the ovarian teratoma (A) CT abdomen showing a right 3 × 3 cm ovarian mass of heterogeneous density, representing a teratoma with fat and calcifications. (B) Gross pathology of a well-encapsulated teratoma. (C) Hematoxylin-eosin stains showing a grade II/III immature teratoma containing immature neural tissue with mitotic figures.**



lance, particularly for conditions like anti-NMDA receptor encephalitis where early recognition and treatment improve the outcome.[1] In this case, the most useful clues to the diagnosis were the presence of seizures, a movement disorder, and hypoventilation following the psychiatric prodrome.

The anti-NMDA receptor syndrome is a type of antibody-positive paraneoplastic limbic encephalitis with antibodies against neural cell membrane antigens. Although the pathogenesis is not completely understood, some reports suggest that the limbic encephalitis results from differences in the host's autoimmune responses rather than from differences in the neoplasm itself.[5] Thus, of particular relevance to the current case, the puerperal period is known to affect various autoimmune disorders. For example, studies have shown that multiple sclerosis often undergoes a relative remission during pregnancy, especially in the third trimester, only to show a higher relapse frequency in the first 4 months postpartum. The mechanisms responsible for this are still unclear.[6] Exacerbations have also been reported following delivery in other antibody-mediated conditions, such as rheumatoid arthritis and myasthenia gravis.[7,8]

A recent publication reported three cases of anti-NMDA receptor encephalitis during pregnancy.[9] The relation between pregnancy and our patient's presentation may be simply coincidental. Alternatively, the impact of sex hormones on the immune system could explain her post-partum presentation. During pregnancy, the maternal immune system is modified to allow immune tolerance to fetal antigens of paternal origin. Studies have shown that estrogen speeds maturation of B cells in the bone marrow, increasing the risk of formation of auto-reactive B cells that escape negative selection.[10] As well, estrogens stimulate antibody production through increased interleukin-10 secretion.[11] Prolactin may also contribute to loss of self-tolerance by decreasing apoptosis of transitional B cells and increasing the lymphocytic response to autoantigens.[10] Thus, increased estrogen and prolactin during pregnancy may promote formation of auto-reactive lymphocytes.

We hypothesize that pregnancy-induced modulation of the immune system may have contributed to our patient's autoimmune encephalitis by a breakdown in tolerance to self-antigen. This observation may stimulate future studies on the pathogenesis of autoimmune antibody production in paraneoplastic disorders. In the meantime, psychiatrists and other physicians should consider the diagnosis of anti-NMDA receptor encephalitis in patients presenting with psychiatric or neurologic symptoms in the postpartum period as early diagnosis is the crucial initial step towards definitive immunomodulating and neoplasm-targeted treatments.

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