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A Rare Case of Anti-NMDA Receptor Encephalitis Associated with an Ovarian Teratoma

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Abstract Anti-N-methyl-D-aspartate (NMDA)-receptor encephalitis is a syndrome of psychiatric symptoms and neurologic sequelae that is commonly associated with an ovarian teratoma. The antagonism of cerebral NMDA receptors disrupts normal brain activity causing acute onset psychological disturbances including mania, psychosis, or anxiety. Due to the rarity of the condition, diagnosis may be delayed as other common disorders such as primary psychiatric disorders or infectious encephalitis are ruled out. With rapid diagnosis and management, including resection of the tumor and immunotherapy, positive outcomes may be achieved. We present the case of a 25-year-old female with neuropsychiatric manifestations and an ovarian teratoma who was subsequently diagnosed with anti-NMDA-receptor encephalitis.

Keywords: *paraneoplastic, anti-NMDA, receptor, encephalitis, ovarian teratoma*

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1. Introduction

Anti-NMDA receptor encephalitis is a potentially fatal form of acute encephalitis caused by an autoimmune reaction against the NR1 subunit of the NMDA-receptor. It was initially described in 1997 by Nokura et al [1] and Okamura et al [2], who reported two separate cases of young women presenting with ovarian teratomas and psychiatric symptoms along with an altered level of consciousness. Both patients experienced a gradual but dramatic improvement in symptoms following tumor removal. In 2005, a series describing four women who also presented with an ovarian teratoma, psychiatric manifestations, altered mental status and central hypoventilation was published. The authors hypothesized that the cause was due to a paraneoplastic process involving an antibody to an unknown antigen that is expressed in the hippocampus [3]. Dalmau et al first discovered these antibodies against NR1/NR2 heteromers in anti-NMDA-receptor encephalitis in 2007 [4]. NMDA receptors have a vital role in neural transmission of synapses, a mechanism susceptible to alteration by anti-NMDA-receptor IgG against the NMDA receptor glutamate subunit, thereby leading to various neuropsychiatric symptoms [4]. Approximately 80% of cases occur in females [5], and the reported median age for onset of symptoms is 21 years, but cases in patients ranging from eight months to 85 years of age have been reported [6,7]. Many patients present with underlying teratomas, which are most commonly ovarian teratomas, although other germ-cell and even non-germ cell tumors have been associated with anti-NMDA-receptor encephalitis [7,8,9]. The overall incidence of the disease remains unknown.

2. Case Summary

Our patient was a 25-year-old female with no significant past medical history who presented with an acute onset of psychosis and catatonia. 24 hours prior to presenting to the hospital, the patient's boyfriend reported that she was acting very "strangely", describing episodes of difficulty communicating and frank mutism. He also described episodes of heavy laughter followed by random bouts of excessive crying and intermittent agitation throughout the day. The patient had no history of psychiatric illness and had never exhibited such behavior before. She was adopted as a child and did have a positive family history of bipolar disorder in her biological family. Routine labs done at an outside hospital were unremarkable, but a pelvic ultrasound was done which showed a left adnexal mass.

Upon presenting to our hospital, the patient was vitally stable but completely unresponsive to voice or sternal rub. On exam, her pupils were equal and reactive bilaterally. Cardiovascular exam showed regular rate and rhythm without any murmurs or added sounds. Lungs were clear to auscultation bilaterally. Abdomen was soft, lax and nontender with no guarding or rebound tenderness. Bowel

sounds were positive. Despite being unresponsive, the patient was able to maintain motor control when her arms were dropped from height. In addition, she did have a slight tremor in her hands bilaterally, stronger in her left arm. Deep tendon reflexes were normal. Labs were unremarkable, including tumor markers CEA, CA 19-9, and CA-125, but her AFP was elevated at 36.7. Her CXR was unremarkable. A CT scan of her chest, abdomen and pelvis with contrast showed a complex 7.8 cm solid-cystic left adnexal mass, concerning for an ovarian neoplasm. The patient was started on olanzapine 5mg BID and lorazepam 1mg QID.

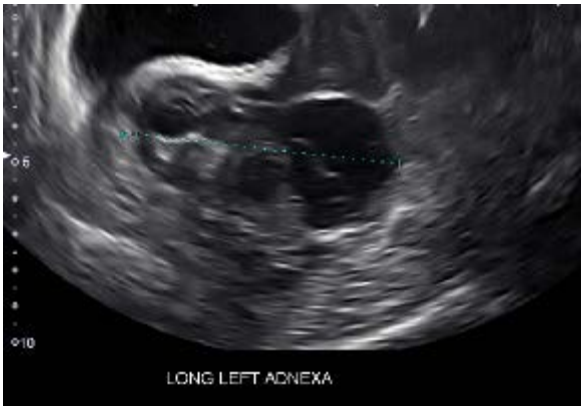

Figure 1. Transabdominal ultrasound in long left adnexa view showing left adnexal mass

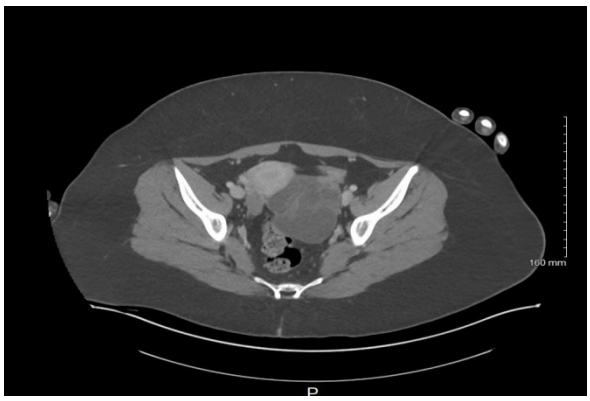

Figure 2. CT Abdomen/Pelvis: 7.8cm solid-cystic left adnexal mass

Roughly 10 hours after she presented, she underwent a left laparoscopic salpingo-oophorectomy with pathology of the removed adnexal mass showing a high grade immature teratoma, but without any malignant sampling of lymph, omentum, or endometrium.

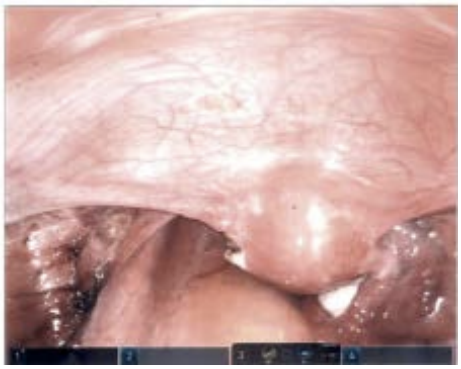

Figure 3. Intra-operative left ovary

She continued to have an altered mental status postoperatively, eventually requiring transfer to the neurological ICU for intubation due to periods of apnea with catatonia and unresponsiveness 3 days after her surgery. Her brain MRI and initial lumbar puncture labs were unremarkable. A vascular catheter was placed for plasma exchange in concordance with a preliminary diagnosis of anti-NMDA encephalitis. The patient completed a course of plasma exchange as well as a 5-day course of IVIG. She was also started on a high dose steroids taper (oral prednisone 60mg daily) for 4 weeks. During her neurological ICU stay, the patient had a tracheostomy tube placed in addition to a PEG tube. She was started on various medications including valproic acid, carbidopa/levodopa, quetiapine, clonazepam and clonidine. She continued to slowly improve over the next 3 weeks and was transferred out of ICU. On the general medical floor, she was gradually able to tolerate the t-piece without any mechanical ventilation. She was still largely unresponsive to commands with the occasional exception of opening her eyes to track people going into her room, which later transitioned into meaningful nods to questions asked by her father. For her autonomic dysfunction, propranolol was initiated and clonidine was tapered off. She was observed on the floors for two weeks during which she showed gradual improvement in her mentation, as she began to follow commands and showed no signs of apneic spells. In terms of her alertness, the patient progressed from following commands to speaking in full sentences. She was decannulated, able to advance her diet and managed to actively participate in physical therapy to a point that she could transfer herself from chair to a walker with assistance. Given the improvement, the patient was deemed fit to be transferred to inpatient acute rehabilitation facility. Her condition gradually improved over the following weeks as her PEG tube was removed, and she was weaned off of prednisone and valproic acid with an eventual return to baseline status several months later.

3. Case Discussion

Clinical features of anti-NMDA-receptor encephalitis can be severe and potentially fatal. The disease often presents initially with non-specific flu-like symptoms such as fever, fatigue or headache and can be misdiagnosed and managed as a flu [10]. Neuropsychiatric manifestations typically follow and have been divided into early and late phase symptoms. Early stage symptoms may gradually present over the course of several weeks and include delusions, hallucinations, agitation, confusion, behavioral changes, memory loss and seizures [11]. Facial twitching and choreoathetosis may also occur as movement disorders in the early stage of the illness. It is quite alarming that up to 77% of patients are initially seen by psychiatrists (due to psychiatric symptoms predominating the presentation) [5], many of which are diagnosed with new-onset primary psychiatric disorders that do not respond to anti-psychotic medications. These patients typically progress abruptly to the late stage of the illness, with symptoms including decreased responsiveness, autonomic instability, urinary incontinence and hypoventilation

[5]. Our patient did not experience flu-like symptoms or early stage symptoms but presented abruptly with severe symptoms and was admitted to the ICU and intubated as life-threatening apneic events were observed, which is the case with a subset of patients [10].

Without a high index of suspicion, the diagnosis of anti-NMDA-receptor encephalitis that is associated with teratomas is typically difficult and time-consuming [12]. Serum and CSF studies to rule out viral and other autoimmune causes of encephalitis, EEG and MRI are indicated in the initial workup. Serum or CSF detection of anti-NMDAR is an important clinical and diagnostic feature of the disease [3]. While brain MRI may show normal findings in up to 67% of patients, 90% of these patients will show abnormalities on EEG [7]. This is due to a vast majority of patients exhibiting nonspecific slowing on EEG at a certain stage during the course of illness [13]. Once a diagnosis of anti-NMDA-receptor encephalitis has been established, further imaging studies including pelvic ultrasound, MRI, CT and/or positron emission tomography are indicated to evaluate the possibility of an underlying teratoma [14]. However, since timely initiation of treatment is associated with better outcomes [7,8], rapidly-deteriorating patients with a high index of suspicion for anti-NMDA-receptor encephalitis may be considered for imaging and removal of the tumor before results for confirmatory antibody studies are obtained, which was our approach for this case. This led to a sustained improvement and excellent outcomes and may very well have been the reason our patient did not deteriorate further or develop more severe neurological symptoms. One series describing patients with anti-NMDA-receptor encephalitis showed that five out of the six patients with an ovarian teratoma who didn't undergo surgery to remove the teratoma died [7]. On the other hand, removal of the teratoma can be curative, with approximately 80% of patients showing substantial neurologic improvement following tumor removal and immunosuppressive treatment [9]. In our patient, symptoms of anti-NMDA-receptor encephalitis gradually improved within a month of removal of the tumor and initiating immunosuppressive treatment, which was consistent with other reported cases. However, it is worth noting that recovery may continue for up to 2 years [7,11].

On review of the literature, combining tumor resection with immunotherapy (corticosteroids, IVIG, and plasma exchange) has been shown to be a superior therapeutic option to immunotherapy alone, and resulted in a more rapid recovery [7,8,9]. To date, there have been no published guidelines to recommend a specific treatment plan, although multiple regimens of immunosuppressive therapy have been described. These generally recommend intravenous steroids and IVIG or plasmapheresis as first-line treatment, while rituximab and cyclophosphamide are second-line therapy [7,9]. Good outcome predictors reported include lower symptom severity (which is assessed as the lack of need for admission to ICU), tumor resection, and prompt initiation of immunotherapy [7].

Prognosis is typically favorable with over 75% of patients showing significant recovery (mean duration of seven months) [7,9]. Clinical improvement usually correlates to a decrease in anti-NMDA antibody titers. However, 20-25% of patients may have relapses that are most commonly observed within the first two years, with some even having a recurrence of ovarian teratoma. Fortunately though, relapses tend to be less severe. The overall mortality rate has been reported at 4-7% with an average of 3.5 months following symptom onset [7,9,15].

With prompt diagnosis and treatment in the form of resection of any underlying teratoma and immunosuppressive therapy, patients with anti-NMDA-receptor encephalitis typically have a high likelihood of a favorable outcome. A multidisciplinary team, including psychiatrists, neurologists, gynecologists and intensivists, must be involved in the process of recognition and management of this disease. This case warrants us to keep our suspicion high for anti-NMDA-receptor encephalitis when a young female presents with acute change in mentation and, if suspected, work up for a possible ovarian teratoma should not be delayed.

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