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Anti-NMDA receptor encephalitis with neurologic sequelae refractory to conservative therapy with complete response to adjuvant therapy

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A B S T R A C T

Background: Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis has been described in increasing frequency in association with benign, mature ovarian teratoma. Affected patients typically present with paraneoplastic limbic encephalitis with flu-like symptoms followed by altered mental status, acute psychiatric symptoms, seizures and amnesia. These symptoms can rapidly progress if not treated aggressively with surgical resection. Profound neurological symptoms may require immunotherapy.

Case: We present a case of anti-NMDA receptor encephalitis associated with a malignant immature teratoma in which symptoms were refractory to surgical management and initial immunotherapy. A complete neurologic response was only seen after initiating adjuvant chemotherapy.

Conclusion: Anti-NMDA receptor encephalitis has rarely been described with immature ovarian teratomas. In these cases, a complete response may not be observed until systemic chemotherapy is started.

1. Introduction

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis has been described in increasing frequency in association with benign, mature ovarian teratoma. Affected patients typically present with paraneoplastic limbic encephalitis with flu-like symptoms followed by altered mental status, acute psychiatric symptoms, seizures and amnesia. These symptoms can rapidly progress leading to obtunded mental status and respiratory depression (Varvat et al., 2010). Early surgical excision of the teratoma is associated with resolution of symptoms and better prognosis (Braverman et al., 2015). Profound neurological symptoms may require immunotherapy. Anti-NMDA receptor encephalitis has been described only rarely with immature ovarian teratomas. We present a case of anti-NMDA receptor encephalitis associated with a malignant immature teratoma in which symptoms refractory to surgical management and initial immunotherapy responded to adjuvant chemotherapy.

2. Case

A 19 year-old college sophomore with no medical history presented to our institution with new-onset confusion, headaches and seizures. Headaches started approximately one week prior to admission. She experienced a seizure and was brought to an outside hospital’s emergency room. In the hospital, she was discharged and brought to our institution. Upon presentation the patient was disoriented, lethargic, and unable to follow commands. A neurological exam was limited by the patient’s mental status. She was admitted and started on valproate sodium and olanzapine for seizure prophylaxis.

Thyroid stimulating hormone, total T3, free T4, anti-thyroglobulin antibody, TSH receptor antibody, thyroperoxidase antibody, and free thyroxin index were all within normal limits. Blood and urine toxicology studies were negative. VDRL titers, West Nile Virus IgG and IgM, Hepatitis A IgM antibody, Hepatitis B surface antigen, Hepatitis C Virus PCR, RPR, HSV-1 and HSV-2 PCR, rapid HIV screen, CMV PCR and EBV PCR were negative. A lumbar puncture demonstrated normal opening pressure, glucose, protein, and no abnormal cells. The patient was started on intravenous acyclovir. Computed tomography of the head showed no abnormalities. On hospital day 4 an MRI of the head was performed under sedation; no significant abnormalities were identified. Rheumatologic evaluation was negative including ESR, serum C3 and C4 complement, anti-smith antibody, anti-smith antibody, anti-RI antibody, and RNP antibody.

A preliminary diagnosis of paraneoplastic encephalitis syndrome was made and anti-voltage gated calcium channel antibody, anti-voltage gated potassium channel antibody, and anti-NMDA receptor antibody were obtained. Anti-NMDA receptor antibody screening was positive. CA-125 was elevated to 73 U/mL and serum AFP was 144.5 ng/mL. Pelvic sonogram showed a large complex and cystic mass of the left adnexa measuring 20.8 × 12.8 × 16.2 cm. A computed...
tomography of the chest, abdomen, and pelvis showed a small, non-specific ground-glass opacification in the right lower lobe of the lung and a large complex pelvic mass with no evidence of distant metastasis, ascites, or lymphadenopathy (Fig. 1).

On hospital day seven, the patient underwent exploratory laparotomy, left salpingo-oophorectomy, pelvic and paraaortic lymph node dissection, omentectomy, and peritoneal biopsies. Findings included a 20 cm left adnexal lesion with frozen section consistent with an immature teratoma. There was no visible evidence of extraterritorial metastasis and the right ovary had a normal appearance. Final pathology demonstrated a grade 3 stage IC immature teratoma.

On postoperative day one the patient remained disoriented, confused, and aphasic. On postoperative day two her speech was spontaneous, but illogical. She was able to move all four extremities spontaneously, but unable to perform goal directed movements. The patient remained on anti-epileptic medications throughout her hospital course.

The patient was unable to comply with baseline pulmonary function tests and therefore was unable to receive bleomycin. Systemic chemotherapy was initiated with etoposide 100 mg/m² and cisplatin 20 mg/m². Within days of the first cycle her speech and concentration improved. Her affect remained flat, but she was able to ambulate and perform goal directed movements. The patient was discharged on postoperative day 8 on a decadron taper, valproate for seizure prophylaxis, and zolpidem.

She received a total of four cycles of adjuvant cisplatin and etoposide. Bleomycin was never initiated due to borderline restrictive lung disease found on DLCO. The patient underwent speech therapy as an outpatient. Baseline mental status was noted four weeks postoperatively. The patient returned to college roughly five months after completion of treatment. She remains without evidence of disease 54 months after diagnosis. She has regained baseline neurological status with the exception of retrograde amnesia including her entire hospital course.

3. Discussion

The NMDA receptor is found mainly in the hippocampus and has a role in learning and memory formation. This is consistent with the findings that most patients with anti-NMDA receptor encephalitis have persistent amnesia related to their illness (Dalmau et al., 2008). The receptor is composed of two subunits: NR1, which binds glycine; and NR2, which binds glutamate. Anti-NMDA receptors are antibodies to the NR1 subunit of the NMDA receptor found in the postsynaptic membrane. Overexcitation of the NMDA receptor leads to seizures and status epilepticus (Sansing et al., 2007). Decreased function of the NMDA receptor is associated with psychosis and encephalitis.

The exact incidence of this autoimmune disorder is unknown, but may present in patients with or without a known tumor. Eighty percent of patients with anti-NMDA receptor encephalitis are female, with a median presenting age of 21 years, with most cases presenting between the ages of 12 to 45 years of age (Kaysen et al., 2013). A review of encephalitis of unknown origin showed anti-NMDA receptor encephalitis to be identified in 1% of patients admitted to an intensive care unit. This is the second most common cause of autoimmune encephalitis in young adults after acute disseminated encephalomyelitis.

Patients with anti-NMDA receptor encephalitis typically present with symptoms consistent with a viral prodrome such as fever, chills, headache, myalgia, nausea, and emesis. Symptoms can acutely worsen within two to four weeks to include cognitive dysfunction and psychiatric symptoms. Up to 77% of patients will initially seek care from a psychiatric specialist and may be misdiagnosed with new onset schizophrenia (Dalmau et al., 2008). In the early phase of the development of neuropsychiatric symptoms, patients may present with confusion, amnesia, anxiety, depression, agitation, hallucinations, and seizures. Late phase symptoms include altered mental status, catatonia, hyperventilation leading to respiratory distress, and autonomic dysfunction.

Initial diagnostic tests are typically performed to rule out infectious etiologies, toxic and metabolic disorders, and autoimmune conditions. These include, but are not limited to, serum testing, cerebrospinal fluid sampling for viral encephalitis, computerized tomography, magnetic resonance imaging, and EEG. There is no role for brain biopsy, as tissue sampling does not provide a definitive diagnosis. The diagnosis is frequently made with positive anti-NMDA receptor antibodies in the serum or CSF. MRI abnormalities are rare in these patients, found in roughly one-third of patients with confirmed anti-NMDA receptor encephalitis. EEG abnormalities are present in roughly 90% of patients; however, the findings are nonspecific (Dalmau et al., 2008). Once the diagnosis is suspected or confirmed, pelvic imaging, including pelvic ultrasound, CT scan, MRI, or PET scan, should be obtained to search for an underlying teratoma.

Early surgical resection of ovarian teratomas has been associated with a more favorable prognosis and may be curative without adjuvant treatment. A literature review and case series found that roughly 75% of patients who receive surgical treatment fully recover or have mild residual symptoms (Acién et al., 2014). After surgical resection or if no tumor is located, immunotherapy consisting of corticosteroids, intravenous immune globulin (IVIG), and plasmapheresis has been found to shorten the duration to recovery. Patients without a detectable tumor have an improved prognosis when kept on immunosuppression for at least 12 months with azathioprine or mycophenolate mofetil. Patients with symptoms unresponsive to standard immunotherapy may respond to cyclophosphamide and rituximab.

Our case is unique in regards to the refractory nature of the neuropsychiatric symptoms after immunotherapy with prompt response to initiation of systemic chemotherapy. The prognosis for patients with early stage malignant ovarian germ cell tumors is favorable when treated with BEP therapy (Rogers et al., 2004). Our patient was unable to receive bleomycin and proceeded with etoposide and cisplatin (EP) therapy. We found one prior case report in which a patient with anti-NMDA receptor encephalitis secondary to immature teratoma showed minimal response to surgery and immunotherapy and received EP therapy due to inability to institute bleomycin for bacterial tracheobronchitis (Dizon et al., 2012). This patient also improved after...
treatment and at the time of the article the patient had regained moderate neurological function. Our patient did not show signs of response until the first cycle of EP therapy. She has not had any seizures since the first hospitalization and has no residual language deficits. She was able to return to college full time and lives independently. Our case reiterates the importance of early diagnosis and surgical intervention and emphasizes the necessity of early medical therapy with immunotherapy and chemotherapy to increase the likelihood of a complete recovery in patients presenting with anti-NMDA receptor encephalitis.

CRediT authorship contribution statement

Aaron Nizam: Investigation, Writing - original draft, Writing - review & editing. Andrew W. Menzin: Writing - review & editing. Jill S. Whyte: Conceptualization, Investigation, Writing - review & editing.

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