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Reversible Paraneoplastic Encephalitis in Three Patients with Ovarian Neoplasms

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Abstract

Anti-NMDA receptor encephalitis is a recently described potentially lethal but treatable disorder that often occurs as a paraneoplastic manifestation of ovarian teratomas. We report three women with this disorder who presented with subacute onset of delirium, seizures and autonomic instability. Anti-NMDA receptor antibodies were detectable in the serum or CSF of each patient. Ovarian masses were detected in two patients, and subsequently excised. In the third patient, an empiric bilateral salpingo-oophorectomy was performed and revealed a microscopic neoplasm. All patients experienced slow reversal of the neurological symptoms following surgery and immunotherapy. Our experience supports that prompt syndrome recognition followed by tumor removal and immunotherapy usually results in neurological recovery.

Keywords

Anti-NMDA receptor encephalitis; ovarian tumors; dermoid; paraneoplastic encephalitis

Introduction

Anti–N-methyl-D-aspartate receptor (NMDAR) encephalitis is a recently described disorder that often affects young women with ovarian teratomas (1-4). An immune-mediated pathogenesis was suggested when antibodies that target the NR1 subunit of the NMDAR were demonstrated (3-4). This is a multistage disease that starts with changes of behavior, mood, and personality, similar to acute psychosis. Soon, patients develop additional neurologic abnormalities such as seizures, decreased level of consciousness, dyskinesias, autonomic instability, and hypoventilation (1-4). Mature and immature ovarian teratomas have been found in association with this encephalitis (1-3). Prompt diagnosis and removal of the tumor is important for improving prognosis and preventing long-term neurologic sequelae. We report on three women diagnosed with paraneoplastic encephalitis in

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association with ovarian tumors who experienced significant neurologic recovery following surgical resection and chemotherapy or immunotherapy.

Case 1

A 34 year old G1P1 with past medical history of irritable bowel syndrome, polycystic ovarian syndrome and obesity developed a persistent frontal headache for seven days, accompanied by a fever and progressive delirium followed by a generalized tonic-clonic seizure. On presentation, the patient's vital signs, physical examination and routine laboratory tests were unremarkable. The cerebrospinal fluid (CSF) showed inflammatory features, specifically a white blood cell count of 30 thousand/μL (97% lymphocytes). Brain magnetic resonance imaging (MRI) revealed bilateral medial temporal lobe hyperintensity. All testing for infectious etiologies, including bacterial and fungal CSF cultures and blood tests for Lyme disease, Epstein-Barr virus and arbovirus, were negative (Table 1).

The patient's symptoms progressed rapidly. She was acutely delirious with active homicidal and suicidal ideations. Her seizures became intractable and resulted in bradycardia, apnea and hypotension. She had minimally-reactive pupils, bucolingual dyskinesias, and non-purposeful movement of her extremities. Tests for autoimmunity and HIV were negative. MRI showed abnormal T2 signaling in the left hippocampus with increased parameningeal enhancement. Pelvic ultrasound and computed tomography (CT) revealed a 6.1x6.0x7.9cm complex left adnexal mass, with cystic and solid components. Serum tumor markers were within normal limits: Ca125 was 16 U/mL, Ca 19-9 was 7 U/mL, alpha-fetoprotein was 1 IU/mL and hCG was <5 U/mL. Serum and CSF tests for NMDAR antibodies were positive. The patient was given broad-spectrum antibiotics and anti-epileptics, and an emergency exploratory laparotomy was performed, revealing a 4 - 5 cm simple-appearing left ovarian cyst. The right tube and ovary appeared normal. A left salpingo-oophorectomy was performed. The patient was transferred to the neurologic intensive care unit where she was intubated and sedated for the next 24 hours. Post-operatively, the patient received one dose of cyclophosphamide and was started on a steroid taper, as well as plasma exchange and intravenous immunoglobulin. Her neurologic symptoms improved. On the seventh post-operative day, the seizure-like activity resolved, and she was weaned off of the ventilator. Upon discharge to a rehabilitation center, she had mild cognitive deficits but was psychiatrically intact. She regained her baseline neurologic function in nine months.

The left ovarian cyst showed an immature teratoma, grade 2. Immunohistochemical stains for glial fibrillary acidic protein (GFAP) and synaptophysin showed strong focal staining. Neurofilament (NFRM) showed weak focal staining. Ki67 showed extensive proliferative activity of the immature glial tissue, focally reactive in 30-40% of the lesional cells.

Given the emergent nature of the procedure, staging was not performed, though there was no gross evidence of extra-ovarian tumor at the time of exploration, rendering this clinical Stage I disease. After discharge, the patient received three cycles of bleomycin, etoposide and cisplatin (BEP) chemotherapy. Post-treatment CT and MRI showed no disease in the pelvis. Tumor markers were all negative. Currently, four years later the patient is well.

Case 2

A 24 year-old G0P0 with a past medical history of migraine headaches presented with short-, and long-term memory loss, panic attacks, confusion and hallucinations. She was admitted to an inpatient psychiatric facility for evaluation and treatment, where her symptoms worsened over the course of the following month. A complete hematologic workup failed to reveal the cause of her symptoms. All testing for possible infectious etiologies, including herpes simplex virus, cryptococcus, West Nile virus, and varicella

zoster virus, was negative. Examination of CSF revealed a white blood cell count of 15 thousand/μL (100% lymphocytes). An electroencephalogram revealed findings consistent with seizure activity, prompting her transfer to our institution.

On presentation, the patient had severe autonomic dysregulation. She was tachycardic at 170 bpm, and hypertensive. She was catatonic, minimally responsive, and displayed diffuse hyperreflexia. Testing for Lyme disease, HIV, cytomegalovirus, parvovirus and hepatitis, as well as autoimmune disease was negative. An MRI demonstrated enhancing lesions in the splenium of the corpus callosum. Although such a lesion can be seen in Marchiafava-Bignami disease, there was no extensive history of alcohol consumption. She was given intravenous steroids, but sbecame obtunded, acutely hypotensive and febrile. Imaging was concerning for spontaneous bowel perforation, which required emergent exploratory laparotomy. At laparotomy, multiple small perforations of the transverse colon were noted. A transverse colectomy was performed, with creation of a right end colostomy and left Hartmann pouch. Additionally, a 9 cm, thin-walled, ruptured left adnexal cyst was incidentally noted. Hair and fatty tissue were noted during the ovarian cystectomy. Histology showed benign cystic teratoma. Testing for antibodies to NMDAR was positive in serum and CSF.

Post-operatively, the patient experienced rapid reversal of her neurologic impairment. She received five plasmapheresis treatments, with significant improvement in her mental status and physical limitations. At discharge, the patient had no further hemodynamic instability, and had a normal psychiatric examination with the exception of complete amnesia of the events immediately preceding her admission. She was able to walk with assistance. The patient was discharged to an acute rehabilitation facility on post-operative day 20.

Case 3

A 53 year-old with a past medical history of depression and anxiety, and a remote history of a seizure disorder, presented complaining of worsening confusion, headaches, and changes in her speech pattern. Subsequently, she developed behavior and personality changes and a precipitous decline in her neurologic status, resulting in continuous abnormal movements, unresponsiveness, hypoventilation, and autonomic dysfunction.

A thorough hematologic evaluation failed to reveal the cause of her symptoms. Testing for infectious etiologies (HIV, RPR, Lyme, HSV, hepatitis and enterovirus) was negative. Serum and cerebrospinal fluid were positive for anti-NMDAR antibodies. MRI of the brain revealed nonspecific bilateral, frontal lesions on the T2-weighted images. EEG showed slow and disorganized activity without epileptic features. A CT of the abdomen and pelvis revealed normal-appearing ovaries bilaterally.

The patient developed persistent autonomic instability, orobucolingual dyskinesias that resulted in tongue laceration, stereotyped motions involving arms and legs (cycling-like movements), dystonic postures, and dissociate responses to stimuli (such as resisting eye opening, but unresponsive to pain). Given the characteristic clinical features of anti-NMDAR encephalitis and the demonstration of these antibodies in the patient's serum and CSF, the decision was made to proceed with a laparoscopic bilateral salpingo-oophorectomy.

Intraoperative evaluation revealed entirely normal-appearing pelvic organs. A bilateral salpingo-ophorectomy was performed. Pathologic evaluation of the ovaries revealed a sex cord stromal tumor, with positive staining for AE 1/3 cytokeratin. Postoperatively, the patient underwent a five-day course of IVIG and methylprednisolone followed by a steroid taper and one dose of cyclophosphamide.

The patient's neurologic condition began to improve in the postoperative period. First, the autonomic instability resolved, and the abnormal movements progressively subsided. After discharge, her personality and behavioral problems, including impulsivity, disinhibition, and poor attention and planning continued to improve. At 18 months after discharge, she was nearly back to normal baseline.

Discussion

Recently, Dalmau *et al* described a new category of autoimmune encephalitis associated with antibodies to the N-methyl-D-aspartate receptor (4-6). This receptor, predominantly expressed in the hippocampus and forebrain, is also expressed by the nervous tissue contained in teratomas. In a case series of 100 patients with anti-NMDAR encephalitis, 58 had an underlying tumor, most commonly an ovarian teratoma (6). As in the cases described above, patients with evidence of these antibodies in their serum or CSF tended to have dramatic and severe symptomatology. All patients presented with psychiatric symptoms or memory problems; 76 of them developed seizures, 69 patients had autonomic instability and 66 of them had hypoventilation. However, despite their initially ominous presentations, patients with these antibodies seemed to have a better prognosis than those with other types of paraneoplastic encephalitis; 75 patients ultimately recovered. The disease usually affects children and young individuals, and rarely occurs in patients older than 50 years or postmenopausal women. (1-2). Florance et al, reported 32 of 81 patients with anti-NMDAR encephalitis (40%) were younger than 18 years, the youngest only 23 months of age (1).

In patients with anti-NMDAR encephalitis and ovarian teratoma, surgical resection of the tumor and subsequent immunotherapy are the treatment modalities with the most significant effect on outcome (6). In Dalmau's case series, patients whose tumor was identified and resected within four months of the onset of symptoms had fewer severe deficits at the conclusion of follow up than the rest of the patients. Therefore, it would seem that early surgery in these patients would be of utmost importance in preventing worsening of neurologic status. In patients with anti-MDAR encephalitis the presence of a tumor (usually ovarian teratoma) is dependent on age, sex and ethnicity, being more frequent above 18 years of age (2). The frequency of ovarian teratomas was 56% in women > 18 years old, but only 31 % in women < 18 years old (1). It remains a subject of debate whether empiric salpingo-oophorectomy should be performed in patients without clinical evidence of a tumor. In patients without radiological evidence of a tumor, our recommendation is immunotherapy followed by periodic tumor screening. Our general treatment approach includes imaging to screen for tumor, usually an ovarian teratoma. If identified, surgical removal is recommended. For younger patients, thorough discussion of the risks and benefits of such a procedure should be undertaken. Surgical menopause with need for hormone replacement therapy, as well as future fertility issues must be balanced with potential for neurologic recovery. Following surgery, immunotherapy including first line treatments such as plasma exchange, IVIG, and corticosteroids are recommended, but second line immunotherapy such as rituximab and cyclophosphamide may be required. Patients with a tumor that may be surgically removed respond faster and better and require second line immunotherapy less frequently than those without tumor. Overall, 75-80% of patients, with or without tumor, have substantial clinical recovery (2).

In conclusion, anti-NMDAR encephalitis is a potentially lethal but treatable condition sometimes associated with ovarian teratomas — both mature and immature. The exact incidence of anti-NMDAR encephalitis is still unknown but it seems to be the most frequent paraneoplastic encephalitis (2). Female patients presenting with new onset of psychiatric and neurologic symptoms should be thoroughly evaluated to rule out underlying neoplasm. In

the event of a diagnosis of an adnexal mass, surgical resection should be performed as soon as possible in an effort to improve neurologic outcomes.

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Abbreviations

NMDA	Anti–N-Methyl-D-Aspartate Receptor
CSF	Cerebrospinal Fluid
GFAP	Glial Fibrillary Acidic Protein
NFRM	Neurofilament
BEP	Bleomycin, Etoposide and Cisplatin
LDH	Lactate Dehydrogenase
AFP	Alpha Fetoprotein
hCG	Human Chorionic Gonadotropin
HSV	Herpes Simplex Virus
EEG	electroencephalography
IVIG	Intravenous Immunoglobulin

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Table 1

Laboratory evaluations

Tests	Case 1	Case 2	Case 3
Cerebrospinal Fluid	30 thousand	15 thousand/ml	
Bacterial culture	No growth	No growth	No growth
Fungal culture	No fungus	No fungus	No fungus
Beta-2-Glycoprotein 1	ND	WNL	ND
Total protein	ND	Mildly elevated	Mildly elevated
Glucose	ND	WNL	WNL
Electrophoresis	ND	WNL	ND
Mercury	ND	WNL	ND
Neuronal cell antibody	ND	WNL	ND
Infection			
Anti-streptolysin O (ASO)	ND	WNL	ND
Lyme disease	Negative	ND	Negative
Ebstein –Barr virus	Negative	Negative	Positive
RPR	ND	Negative	Negative
Anti-Hepatitis B Surface antigen	Negative	Negative	Negative
Herpes simplex	ND	Negative	Negative
Cryptococcal antigen	ND	Negative	Negative
West-Nile	ND	Negative	ND
Varicella-Zoster	ND	Negative	Negative
Arbovirus	Negative	Negative	ND
HIV	Negative	Negative	Negative
Rubeola	ND	Negative	ND
Anticardiolipine antibody	ND	Negative	ND
Diluted Russels Viper Venom test	ND	Negative	ND
Blood culture	No growth	No growth	No growth
Autoimmune panel			
Sjogren antibody (SSA)	Negative	Negative	ND
Sjogren antibody (SSB)	Negative	Negative	ND
Antithyroid peroxidase antibody	Negative	Negative	Negative
Antithyroglobulin antibody	Negative	Negative	Negative
Anti DNA antibody	Negative	Negative	ND
Rheumatoid factor	Negative	Negative	ND
Anti-nuclear antibody	Negative	Positive	Negative
C-Anca	Negative	Negative	ND
Anti-Smith	Negative	Negative	
Anti-RNP Ribonuclear protein	Negative	Negative	
Tumor markers			
CA-125	WNL	WNL	ND
CA 19-9	WNL	WNL	ND

Tests	Case 1	Case 2	Case 3
Serum AFP	WNL	WNL	ND
LDH	WNL	WNL	ND
Quantitative serum beta-hCG	<5 IU/ml	<5 IU/ml	ND
Serum Anti-NMDA receptor antibodies	Positive	Positive	Positive
Cerebrospinal fluid Anti-NMDA abs	Positive	Positive	positive
Miscellaneus tests			
Serum methylmalonic acid	ND	WNL	ND
Lead (blood)	ND	WNL	ND
Urine porphyrins	ND	WNL	ND

Abbreviations: NMDA= Anti-N-methyl-D-aspartate, ND=Not done, WNL=within normal limit, CSF=cerebrospinal fluid, AFP=Alpha-fetoprotein, LDH=Lactate dehydrogenase