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Case Report

Anti-NMDA-Receptor Encephalitis: An Adolescent with an Ovarian Teratoma

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Abstract. *Background:* Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis has been reported to be associated with ovarian teratomas. In many patients, surgical excision has resulted in improvement.

Case: A previously healthy 14-year-old girl presented with confusion which later evolved into a comatose state. Imaging revealed an adnexal mass which was surgically removed and confirmed to be a mature teratoma. Her cerebral spinal fluid was positive for antibodies to NR1/NR2 heteromers of NMDA receptors.

Comments: Cystic teratomas are one of the most common benign ovarian lesions in children and young women. While an association of ovarian teratomas and paraneoplastic encephalitis is published in the neurologic literature, this association needs to be clarified for the practicing gynecologist who may be asked to consult on these patients.

Key Words. ovarian teratoma—encephalitis—paraneoplastic—adolescent—NMDA

Introduction

A specific type of paraneoplastic limbic encephalitis (PLE) has been associated with ovarian teratomas. This devastating clinical picture consists of young women who typically present with initial symptoms of a viral or flu-like illness which progresses into short-term amnesia and psychiatric symptoms such as personality changes, hallucinations, aggressive behavior, or catatonia. They typically develop dyskinesias and seizure-like activity with most women becoming hypoventilatory. After a comprehensive workup to exclude a neurologic, psychiatric, or infectious etiology, full body imaging is done to evaluate for a paraneoplastic syndrome. Ovarian teratomas have been discovered to have antigenic neural tissue with antibody formation which cross-reacts to the N-methyl-D-aspartate (NMDA) receptor in the hippocampus.[1] Improvement has been noted in almost all accounts with removal of the ovarian teratoma and some form of immunotherapy. This recent correlation has been mostly reported in the neurologic literature. Heightening the awareness of the link between PLE and ovarian teratomas is needed since gynecologists may be consulted to perform an ovarian cystectomy or oophorectomy for these patients.

Case

A previously healthy 14-year-old girl initially presented to an outside hospital with symptoms of restlessness, agitation, and incomprehensible speech. The family reported no prior medical condition and stated that her only complaint was nausea and vomiting three days prior to admission. Two days later, she had a brief episode of confusion which led to her evaluation in the emergency room. There, she was noted to have continued agitation and would wander around the emergency room. On arrival to the inpatient unit, she would hallucinate and pretend to talk on the phone. Empiric antibiotics of acyclovir, azithromycin, and ceftriaxone were started after blood work was obtained with a tentative diagnosis of infectious encephalitis. Within two days of admission, she was unable to recognize any of her family members. Her speech became unintelligible and her mental status waxed and waned. She had tremors and involuntary movements of her extremities bilaterally. She was started on intravenous immunoglobulin (IVIG). Over the next three days, her mental status continued to

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decline. Empiric methylprednisolone was started for three days of treatment. Her initial workup included an infectious panel which included EBV, mycoplasma, CMV, HSV, VZV, HIV, mumps, hepatitis panel, West Nile, and enterovirus which were all negative. CSF analysis was unremarkable except for the presence of oligoclonal bands which was an inconclusive pattern. Over the following week, she continued to have decreased mental status and increased choreiform movements and posturing. She was sedated due to her pronounced movements and was then intubated and later received a tracheotomy. She had her first febrile episode of 40 °C on hospital day fifteen but all cultures tested were negative. Magnetic resonance imaging (MRI) of the brain was obtained with the only finding concerning for potential pansinusitis. The patient was then transferred to St. Louis Children's Hospital for further management and possible plasmapheresis.

Prior to this episode, the patient was an active high school freshman with excellent grades. She had no prior medical history and no travel outside of the country. She did not have any recent, new exposures to chemicals, pets, drugs, or alcohol to anyone's knowledge. Her gynecologic history included menarche at age ten with regular menses. There was no history of any endometriosis or prior ovarian cysts, including ovarian teratomas. Her family was not aware of any sexual activity. On arrival, the patient was admitted to the intensive care unit, intubated, and placed on ventilatory support. Plasmapheresis treatment was started. A full body CT was obtained to effectively rule out any evidence of occult malignancy (paraneoplastic syndrome). A 7.3 × 6.8 cm complex left ovarian mass was found and most likely a cystic teratoma. At this time, the gynecology service was consulted. Gynecologic physical exam findings included normal external genitalia development, an intact hymen, and a single digital exam confirming a normally palpated vaginal vault, cervix, and uterus. Mild adnexal fullness was noted on the left. Serum tumor markers included LDH-534 IU/L (100-250 IU/L), beta hCG <5.0 IU/L (0.0-5.0 IU/L), CA-125 - 13.7 U/ml (0.0-30 U/ml), and AFP- 5.8ng/m (0.0-8.1 ng/ml). Of note, the LDH level was mildly elevated but not at levels commonly seen with immature teratomas. CSF was positive for antibodies to NR1/NR2 heteromers of NMDA receptors. Serum levels of these antibodies were not obtained due to her treatments of IVIG and plasmapheresis given prior to her known teratoma. Given the supporting literature to suggest the possible correlation of anti-NMDA-receptor encephalitis, and the large tumor burden with no visible normal ovary, the patient underwent a left salpingo-oophorectomy via laparotomy. The surgical procedure was uncomplicated.

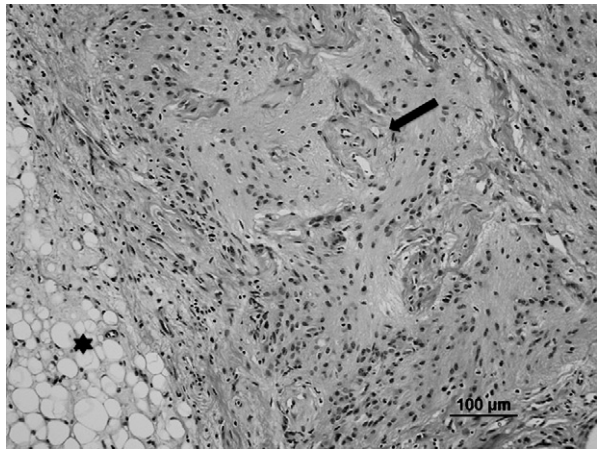

Fig. 1. Ovarian teratoma at 20× with H&E staining. Arrow indicates presence of mature neural tissue components. Asterisk indicates presence of fat.

The right ovary and tube were identified and appeared to be completely normal. Surgical pathology review indicated a 9.5 × 7.5 × 5.5 cm mature ovarian teratoma consisting of heterologous elements including central nervous system tissue, skin, respiratory tract, fat, salivary gland, colon, hair, cartilage, and putative bone (Fig. 1). There was no evidence of immature elements or malignancy. The fallopian tube contained paratubal cysts ranging from 0.3 cm to 0.8 cm and was otherwise unremarkable.

Postoperatively, the patient had no change in her clinical course and remained febrile and comatose. Further testing included a normal echocardiogram and EEG with generalized slowing and no definite epileptiform activity. Another round of plasmapheresis was performed with no change. Rituximab was started with only four doses tolerated due to a declining CD19 count. In her fourth hospital month, she was gradually able to undergo tracheotomy collar trials and tolerate tracheotomy capping during the day. A feeding gastrostomy tube was placed. Throughout her hospital course, the patient was sedated for agitation and involuntary movements. She was eventually placed on valium. Additionally, she would undergo temperature spikes intermittently with no infectious etiology found. Several various courses of antibiotics were attempted and made no improvement. In the end, the etiology for these fevers was thought to be due to an autonomic storm. Approximately three months after dermoid removal, the patient was discharged to an extended care facility with no change in her mental status and lessened sedation for control of choreiform movements.

Nine months after her ovarian teratoma removal, the patient is now living at home with her family. She maintains her gastric tube but is able to tolerate oral intake including crushed food, yogurt, and

drinking thickened juice. Her tracheotomy tube has been removed. She is able to speak in three-word phrases. Motor coordination is inhibited by her choreoathetoid movements and tremors; however, she is now able to throw and catch a ball. She has undergone bilateral Achilles lengthening for her tight heel cords and has recently been able to take her first steps. Current medications include trazodone and valproic acid.

Summary and Conclusion

Ovarian teratomas are one of the most common benign ovarian tumors in women of reproductive age.[2,3,4] Both mature and immature ovarian teratomas have been associated with anti-NMDA-receptor encephalitis.[3,4,5] The ovarian teratoma has neural tissue consisting of NR1 and NR2 subunits of the NMDA receptor which likely acts as antigenic material. Antibodies of these subunits are formed and circulate in the serum or CSF where it is then able to bind to the NMDA receptor located in the cell membrane of hippocampal and forebrain neurons. This antibody is the anti-NMDA-receptor antibody and it is speculated that either this ectopic expression of NR1/NR2 subunits causes failure of immune tolerance or a viral-like illness causes the abnormal immune response.[1–3] The interaction of the NMDA receptor and antibody is thought to be antagonistic and causes a decrease in GABA release. This has been the suggested reason for symptoms such as psychotic behavior, autonomic dysfunction, and dystonia/orofacial movements.[5,6]

The clinical symptoms published have generally followed a progression categorized into five phases described by Iizuka et al.[6] The prodromal phase consists of some kind of cold or viral-like symptoms which were followed by psychobehavioral symptoms over the course of several days. The psychotic phase incorporates a collection of emotional disturbances, cognitive decline, and schizophrenia-like symptoms. The unresponsive phase usually involves being mute, akinetic, and in a catatonia-like state. The hyperkinetic phase has included orofacial-limb dyskinesias ranging from jaw movements and lip chewing to athetoid dystonic movements and choreiform motion of the arms. The final phase is gradual improvement which is thought to occur within months and a full recovery within three or more years. Other common symptoms have included autonomic instability (hyperthermia, labile blood pressures, diaphoresis, and bradycardia or tachycardia), hypoventilation, and seizures.[4,5]

Diagnostic tools have included the following: serum and CSF analysis of anti-NDMA receptor antibodies; EEG assessment with diffuse slowing; CSF analysis with pleocytosis (elevated white blood cell count), an elevated protein level, and oligoclonal bands; and MRI imaging with abnormal signaling in the medial temporal lobes.[7] In a series of 100 patients diagnosed with anti-NMDA receptor encephalitis, 77% had an EEG with generalized slowing with non-epileptic discharges, 91% had evidence of pleocytosis in CSF analysis, and only 55% had abnormal MRI findings. 59% had a tumor discovered and of the tumors found, the most common was an ovarian teratoma.[6] Teratomas are found to be bilateral 15% of the time and totipotential cells in the ovary can make this a much more susceptible location. Imaging modalities assist in determining this prior to potential surgical management.[3,6]

Treatment outcomes have varied. In some patients, surgical removal of the associated tumor was associated with more rapid recovery compared to those without surgery. Interestingly, both groups of surgical and nonsurgical patients showed improvement.[4] There is no data in the limited published literature specifying whether an ovarian cystectomy or oophorectomy is preferred. Total removal of the tumor burden is recommended. Various types of immunotherapy have been used including intravenous immunoglobulin, plasmapheresis, and corticosteroids.[4–7] When unresponsive to these therapies, cyclophosphamide and rituximab have been administered because of their effectiveness in other immune-mediated CNS disorders.[6] The prognosis is, overall, favorable with many reports of clinical improvement ranging from a slow period of ventilation required for 6-9 months noted without surgical tumor resection to a dramatic clinical improvement within days after surgical tumor resection.[1,4]

Our case followed a very similar clinical picture as presented in the current literature. Diagnostic testing included a positive CSF anti-NMDA receptor antibody testing. CSF analysis showed the presence of oligoclonal bands. EEG findings indicated diffuse slowing. Our case did not show MRI imaging with abnormal mediotemporal lobe signaling. Initially, our patient did not show much improvement three months after her surgery; however, nine months from her ovarian teratoma removal, she has made progress.

With recent developments in further investigating this diagnosis, it is speculated that this type of paraneoplastic limbic encephalitis is under-diagnosed. Thus far, the majority of anti-NMDA receptor encephalitis cases have involved very young women with ovarian teratomas.[3,6] With the evolving case studies and series being published in the neurologic literature, it is important to increase awareness of this diagnosis within the gynecologic community. Gynecologists may be consulted to perform oophorectomies or ovarian cystectomies for patients with such

neurologic symptoms who are found to have teratomas by imaging studies.

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