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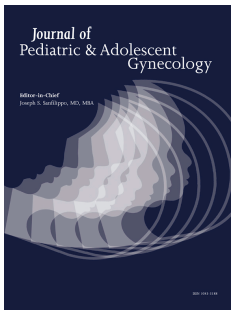

Ovarian Teratoma Associated with Coexisting anti-N-Methyl-D-Aspartate Receptor and Glial Fibrillary Acidic Protein Autoimmune Meningoencephalitis in an Adolescent Girl: A Case Report

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PII: S1083-3188(17)30540-5

DOI: 10.1016/j.jpag.2017.12.009

Reference: PEDADO 2192

To appear in: *Journal of Pediatric and Adolescent Gynecology*

Received Date: 27 November 2017

Accepted Date: 21 December 2017

Please cite this article as: Martin AL, Jolliffe E, Hertweck SP, Ovarian Teratoma Associated with Coexisting anti-N-Methyl-D-Aspartate Receptor and Glial Fibrillary Acidic Protein Autoimmune Meningoencephalitis in an Adolescent Girl: A Case Report, *Journal of Pediatric and Adolescent Gynecology* (2018), doi: 10.1016/j.jpag.2017.12.009.

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Title: Ovarian Teratoma Associated with Coexisting anti-N-Methyl-D-Aspartate Receptor and Glial Fibrillary Acidic Protein Autoimmune Meningoencephalitis in an Adolescent Girl: A Case Report

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Keywords: ovarian teratoma; anti-NMDA receptor encephalitis; glial fibrillary acidic protein (GFAP) meningoencephalitis; autoimmune meningoencephalitis

Acknowledgements

The authors received no funding for the research described in this manuscript.

The authors would also like to acknowledge the Mayo Clinic Medical Laboratories for their cerebrospinal fluid evaluation in this patient.

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Abstract

Background: Ovarian teratomas are rarely associated with paraneoplastic autoimmune meningoencephalitis. In addition to the well-known N-Methyl-D-Aspartate Receptor (NMDA-R) antibody, the glial fibrillary acidic protein (GFAP) antibody is a novel biomarker of autoimmune meningoencephalitis that may be seen in patients with ovarian teratoma.

Case: A 13-year-old girl with acute-onset meningoencephalitis and incidental finding of ovarian teratoma was found to have co-existing anti-NMDA-R and GFAP antibodies present in her cerebrospinal fluid (CSF).

Summary and Conclusion: NMDA-R and GFAP autoimmune encephalitis should be considered in adolescent patients with neurologic or psychiatric symptoms and an ovarian teratoma. Prompt diagnosis and surgical resection increase the likelihood of full neurologic recovery.

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Introduction

The most common ovarian neoplasm found in adolescents is the mature cystic teratoma, accounting for up to 50% of pediatric tumors[1]. These tumors may contain tissue derived from all 3 germ cell layers. An estimated 30-50% contain neural tissue[2], which has been implicated in rare cases of paraneoplastic encephalitis. It is theorized that exposure to the ectopic neural tissue leads to autoimmune production of antibodies targeting receptors in neurons responsible for memory and learning in the hippocampus and forebrain[3].

The first report of an association between ovarian teratomas and an autoimmune central nervous system (CNS) disorder was in 2005. The suggested etiology was an autoimmune hippocampal antigen, which was later identified as the N-Methyl-D-Aspartate Receptor (NMDA-R)[4]. The NMDA-R is a glycine and glutamate ligand-gated cation receptor, which participates in excitatory synaptic transmission. Antibodies produced in response to the neural component of an ovarian dermoid can bind this receptor and lead to encephalitis[3]. Case reports and observational studies have estimated that 36-50% of patients with anti-NMDA-R encephalitis have an ovarian teratoma[4,5].

Antibodies to an intermediate filament found in astrocytic cytoplasm, glial fibrillary acidic protein (GFAP), were recently identified as a novel marker of autoimmune meningoencephalomyelitis[6]. Though serum GFAP positivity has been reported in multiple pathologies such as gliobastoma multiforme, glioma, traumatic brain injury, and autism, GFAP cerebrospinal fluid (CSF) positivity is highly specific for autoimmune CNS disorders[7]. GFAP astrocytopathy can present with a wide range of psychiatric,

meningeal and myelopathic symptoms[6]. Other reported hallmarks include optic disc edema and radial linear periventricular enhancement on magnetic resonance imaging (MRI)[7]. Initial studies also report an association with neoplasia, with ovarian teratoma in 6-14% of patients with GFAP astrocytopathy[6,7].

We report the case of an adolescent girl with an ovarian teratoma associated with coexisting anti-NMDA-R and GFAP autoantibodies in her CSF presenting with acute-onset meningoencephalitis.

Case

A developmentally appropriate 13-year-old girl presented to the emergency department complaining of intractable headache associated with photophobia, phonophobia, nausea and vomiting, and decreased appetite for four days. She was febrile to 39.3 degrees Celsius. A rapid group A strep throat culture was positive and she was started on Amoxicillin. She was alert and following commands with no neurologic deficits or signs of meningismus. She had mild pharyngeal erythema and submandibular lymphadenopathy. She was admitted with concern for meningitis verses encephalitis. Pediatric neurology was consulted and headaches continued despite multiple medications. Computed tomography (CT) head, magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) of the brain were normal. MRI of the spine showed a 3.5 x 2.2 cm benign-appearing right adnexal cyst. Lumbar puncture was significant for a lymphocytic pleocytosis with 204 white blood cells/μL and 91% lymphocytes, elevated protein at 124 mg/dL, and increased opening pressure (33 cm H_2O) concerning for viral

meningitis. She received a ceftriaxone, vancomycin, and acyclovir until CSF bacterial, viral and fungal studies returned negative. Systemic infectious and rheumatologic evaluations were also negative. She was started on acetazolamide for elevated opening pressure.

Four days later, her headache continued and she developed agitation, insomnia, diplopia, vertigo, abdominal pain, generalized myalgias, leg weakness and difficulty walking. Physical exam was notable for disinhibition, perseveration, dysarthria, vertical binocular diplopia, generalized hyperreflexia with asymmetric clonus, and ataxic gait without lower extremity weakness. Repeat CT head was normal. Continuous video electroencephalogram (EEG) showed no epileptiform activity but did reveal diffuse generalized slowing suggestive of encephalopathy. The differential diagnosis at this time included post-infectious autoimmune encephalitis, acute disseminated encephalomyelitis (ADEM), and meningoencephalitis. Repeat laboratory blood evaluation was unremarkable. Repeat CSF was positive for oligoclonal banding and a normal IgG index of 0.5. Flow cytometry was normal. NMDA-R antibodies were detected in the CSF, but not in the serum. Serum protein electrophoresis, myeloperoxidase IgG and proteinase 3 IgG were normal. She received intravenous methylprednisolone 20 mg/kg daily for five days with some improvement in gait, but otherwise minimal change. She received three of five plasma exchanges, which were discontinued due to a central line-associated blood stream infection with methicillin-sensitive staphylococcus aureus (MSSA). She then received two intravenous immunoglobulin (IVIG) 1g/kg infusions with improvement in symptoms. She was ultimately discharged home on hospital day 34 with significant

improvement in neurologic status and plans to continue clonidine and olanzapine for dysautonomia and agitation, respectively.

Following discharge, CSF studies returned positive for GFAP autoantibodies, which prompted performance of an abdominal ultrasound to evaluate for the presence of an ovarian teratoma. A 2.4 x 2.1 x 1.6 cm right ovarian complex cystic structure with an echogenic focus consistent with a dermoid tumor (Figure 1) was noted. She underwent laparoscopic ovarian cystectomy (Figure 2). Final pathology showed a mature teratoma containing mature glial tissue involved by a T-cell lymphocytic infiltrate, suggesting a likely nidus of disease (Figure 3). At a 2 month follow-up, she was being weaned off of clonidine and olanzapine, reported drastic improvement in her neurologic symptoms and was working with speech therapy on short term memory difficulty.

Summary and Conclusion

This report describes the case of an adolescent girl with acute-onset meningoencephalitis. The discovery of the associated teratoma was made when gynecology was notified of the presence of anti-NMDA-R and GFAP antibodies in her CSF. Confounding the clinical picture was a recent diagnosis of group A streptococcal pharyngitis, which was initially thought to be the etiology of a post-infectious autoimmune encephalitis. Making the diagnosis of paraneoplastic autoimmune encephalitis is difficult. Indeed, the differential diagnosis for the neurologic and psychiatric symptoms seen in our patient is wide and includes infectious, neoplastic, paraneoplastic, autoimmune, vasculitic, traumatic, toxic and metabolic etiologies. Presenting symptoms for both NMDA-R and GFAP

autoimmune meningoencephalitis can include headache, behavioral and cognitive changes, altered mental status, seizures, vision changes, movement disorder, ataxia, gastrointestinal symptoms and weight loss[3,6,8]. Both NMDA-R and GFAP antibodies have been associated with underlying neoplasm, most commonly ovarian teratoma. When NMDA-R and GFAP coexist, the likelihood of underlying neoplasm is increased [6,7]. Identification of either antibody should prompt evaluation for an underlying neoplastic process.

Few cases of concurrent ovarian teratoma and meningoencephalitis with CSF positivity for GFAP IgG with or without NMDA-R autoantibodies have been reported in the neurology literature. In a retrospective review of 16 patients with GFAP meningoencephalitis, there were 2 cases of co-existing NMDA-R autoantibodies in CSF. One of these had an ovarian teratoma and neither had classic NMDA-R encephalitis[6]. Another retrospective study of 102 patients with GFAP-IgG positivity of serum, CSF or both, found that 22% of cases were also positive for NMDA-R-IgG. Of those with co-existing GFAP-IgG and NMDA-R-IgG, 8 ovarian teratomas were identified[7].

The treatment for anti-NMDA-R encephalitis with an ovarian teratoma is tumor excision with or without immunotherapy[3,8]. Reported outcomes include full neurologic recovery, mild to severe deficits, and death. Outcomes depend on the rapidity of diagnosis and resection. Rates of neurologic recovery in patients undergoing early resection are reported to be 72-92%[3,8]. Though there is little information on treatment and outcomes of GFAP meningoencephalitis, it has been suggested that the multiplicity of neural antigens

in ovarian dermoids drive the immune response against both NMDA-R and GFAP[6]. Therefore, teratoma resection is also likely to be beneficial in GFAP meningoencephalitis.

Though the relationship between ovarian teratomas and NMDA-R encephalitis has been established for more than a decade, there is little knowledge among gynecologic surgeons regarding the association of ovarian teratomas with the novel GFAP antibody. Awareness of this exceedingly rare entity among pediatric and adolescent gynecologists is critical as rapid diagnosis and surgical resection likely portend the best prognosis.

Conflicts of Interest

The authors report no proprietary or commercial interests in any product mentioned or concept discussed in this article.

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Figure Legends

Figure 1. Abdominal ultrasound showing 2.4 x 2.1 x 1.6 cm right ovarian complex cystic structure with an echogenic focus consistent with a dermoid tumor.

Figure 2. Gross specimen of ovarian teratoma following laparoscopic resection.

Figure 3. Histologic slides showing mature glial tissue component of teratoma with inflammation in low (A) and high (B) powered views. Lymphocytes stained positive for CD3, indicating a T-cell lymphocytic infiltrate (C).

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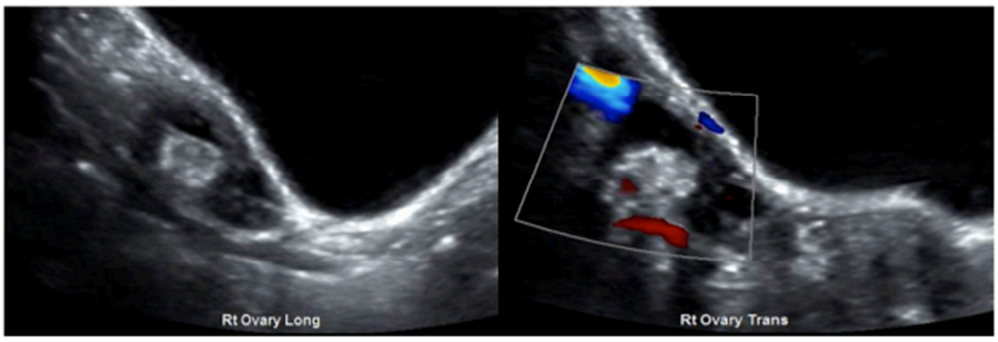

Figure 1. Images from abdominal ultrasound showing complex, right ovarian cyst consistent with an ovarian dermoid.

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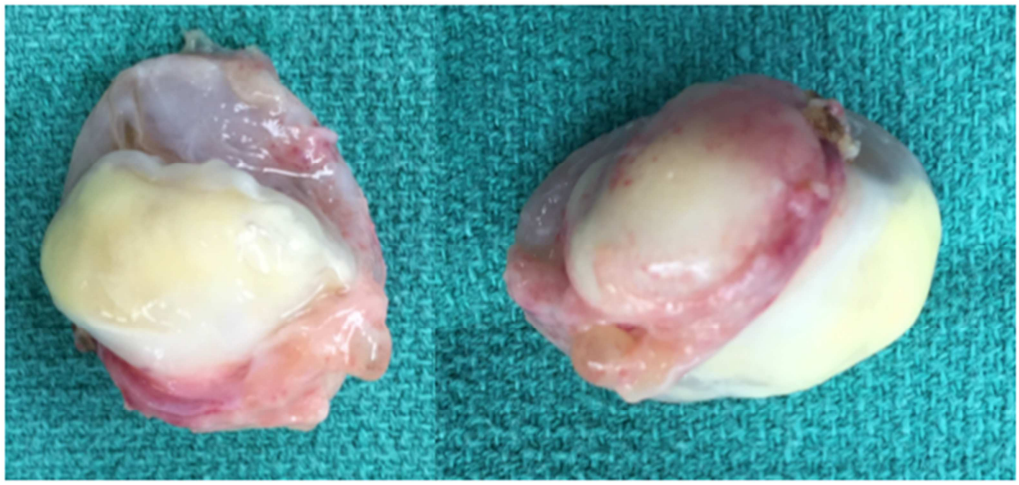

Figure 2. Two views of gross specimen following laparoscopic resection of mature ovarian teratoma.

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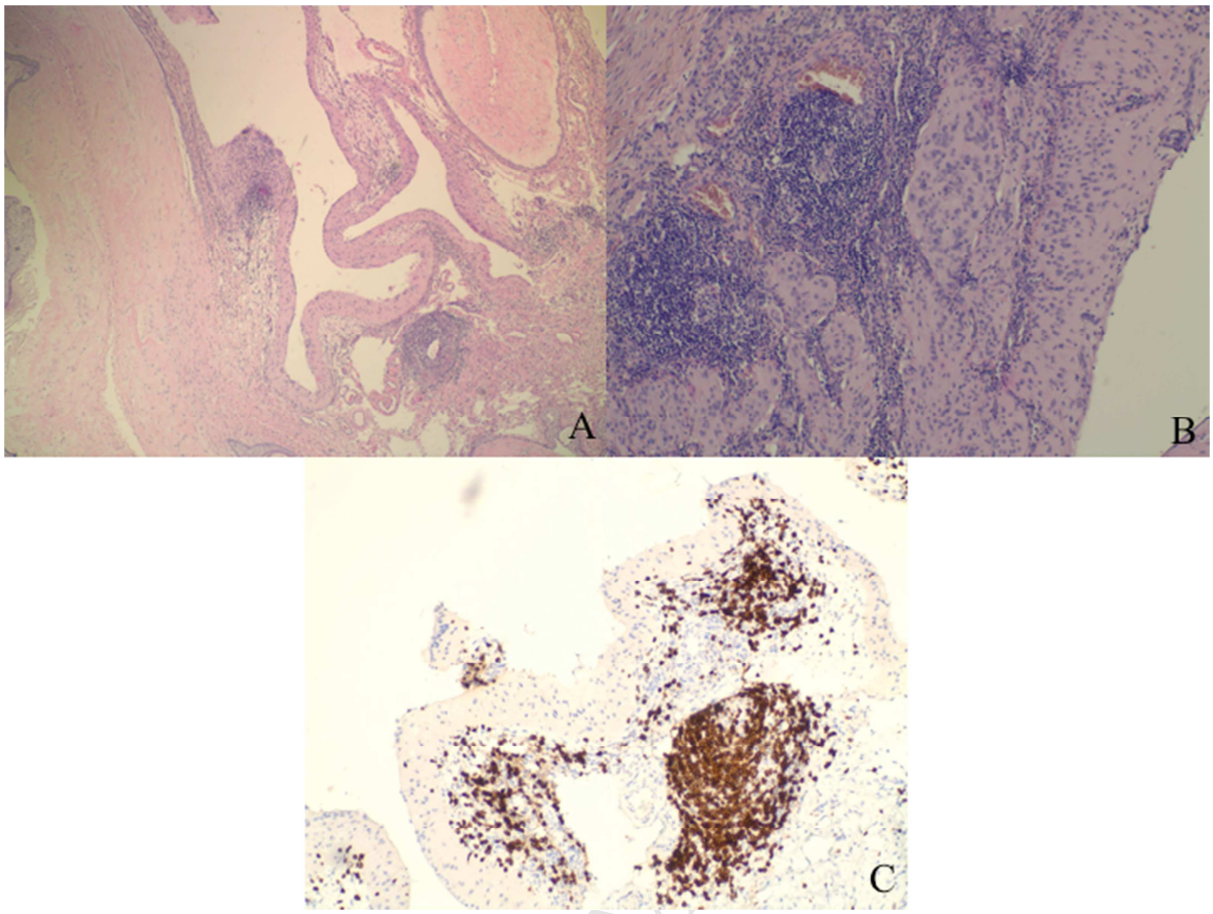

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