Novel Insights from Clinical Practice

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Immune-Mediated Encephalitis and Virilization in Association with a Mature Cystic Ovarian Teratoma in an Adolescent Girl

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Established Facts

- Mature teratomas are the most common type of ovarian tumor in the pediatric population, and are mostly benign and nonsecreting.
- Auto-immune encephalitis is a rare manifestation of ovarian teratomas and has been described in young women and adolescents. This is thought to be caused by the immune cross-reactivity between the tumor elements and hippocampal antigens such as the N-methyl-D-aspartate receptor (NMDAR).

Novel Insights

- Virilization can occur from an ovarian teratoma in children and adolescents as reported in our patient. The few androgen-secreting teratomas reported in the literature are all described in postmenopausal women and prepubertal girls.
- This is the first case report of the association of both virilization and immune-mediated encephalitis with an ovarian teratoma in the same patient, which is even more unique due to its presentation in the pediatric age group.
- The diagnosis of unexplained encephalitis in a young girl should raise the suspicion of an immune-mediated phenomenon and should prompt the physician to rule out the presence of an ovarian teratoma.

Key Words
Immune-mediated encephalitis · Teratoma · Virilization · Adolescent girl

Abstract

Background: Mature cystic teratomas are the most common form of ovarian tumor in children and adolescents. These tumors are mostly benign and non-secreting. Virilization from an ovarian teratoma is exceptionally rare in pediatrics. Equally rare is the association of ovarian teratomas with auto-immune encephalitis. ***Methods:*** We describe the case of a 15-year-old girl with menstrual abnormalities and virilization, who had a past medical history of encephalitis of an unknown etiology 16 months prior to presentation. ***Results:*** Endocrine evaluation revealed an elevated serum testosterone and 17-hydroxy progesterone. A large left ovarian tumor was seen on a CT scan. Surgical excision revealed a mature

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cystic teratoma containing 6 liters of clear fluid with high androgen levels. Antibodies to the N-methyl-D-aspartate receptor of the hippocampus were detected in pre-operatively archived serum, but undetectable 6 months postoperatively. Immunohistochemistry studies on the tumor sections revealed that the antibodies in the patient's serum reacted with areas of the tumor expressing the N-methyl-D-aspartate receptor. Postoperatively, the patient's menstrual cycles became regular and her behavioral problems resolved. Her testosterone levels fell precipitously as well. ***Conclusion:*** Both virilizing mature cystic teratomas and teratoma-associated encephalitis are extremely rare in the pediatric population. We report on the first instance of these 2 rare entities occurring in the same patient.

Case Report

In March 2007, a 15-year-old female presented with a history of irregular menses at the endocrinology clinic of the Children's Hospital at Montefiore. Menarche was reported to be at age 12. Over the past year, her menstrual cycles had been highly irregular with some more prolonged than usual. She had also noticed a deepening of her voice, increased facial and body hair, and significant weight gain (20 kg) over the last year. She weighed 62.3 kg (75th percentile) and was 155.8 cm tall (10–25th percentile). Physical examination was significant for a deep masculine voice, mild hirsutism (especially along the linea alba and over the thighs; Ferriman-Galloway score of 10) and mild facial acne. Abdominal examination revealed a large solid mass obscuring the costal margins. Her pubertal staging was Tanner 5 for breast and pubic hair. She also had significant clitoromegaly measuring 2 × 1.5 cm, with a normal introitus.

The patient's past medical history was significant for a hospital admission for encephalitis approximately 16 months prior to presentation. During that admission, she presented with a 3-day history of altered mental status and severe behavioral abnormalities including inappropriate laughter and crying, difficulty recognizing her parents, and auditory and visual hallucinations. She initially had 3 brief seizure-like events. Over the next few days, she exhibited highly aggressive behavior requiring restraints. During the episode of encephalitis, her work-up revealed normal blood count, electrolytes, glucose and liver function tests as well as negative urine toxicology screen. Cerebrospinal fluid (CSF) studies revealed pleocytosis with no other abnormalities, and 3 consecutive MRIs during the hospitalization were negative for any intracranial mass lesion or bleed. A complete encephalitis panel including serology for tuberculous meningo-encephalitis, cat-scratch disease, Epstein-Barr virus, cytomegalovirus, mycoplasma, bordetella, cryptococcosis, HIV ELISA and herpes simplex virus PCR was negative. An electro-encephalogram showed a left temporal spike and a wave pattern with intermittent polymorphic slowing as well as right temporal continuous polymorphic and rhythmic slowing.

A diagnosis of encephalitis of unknown etiology was made. She was placed on dilantin for the seizures and then later weaned off and placed on carbamazepine, as well as Abilify (aripiprazole) for her mood swings and anxiety. Her mental status remained unchanged. She responded transiently to a 5-day course of intravenous immunoglobulin and was able to talk coherently. She was re-hospitalized a few weeks later for severe aggression and psychotic behavior that again responded marginally to intravenous immunoglobulin. After discharge, she was stable but still continued to have mood swings and difficulty sleeping.

Endocrine work-up revealed elevated serum androstenedione, dehydroepiandrosterone, testosterone and 17-hydroxyprogesterone (table 1). Pelvic and abdominal sonograms demonstrated a large complex cystic mass occupying most of the abdomen and containing dependent debris thought to represent a functional ovarian cyst. The uterus appeared normal. A CT scan of the abdomen with contrast confirmed a huge tumor occupying most of the abdominal cavity measuring 17.8 × 21.7 × 18.8 cm in size. The tumor was seen to arise from the left ovary with a 6-cm-long pedicle. The left ovary was small, roughly measuring 1.6 × 1.7 cm in size. The right ovary was slightly prominent measuring 4.1 × 2.5 × 4.0 cm in size with follicles. No lymphadenopathy or free fluid was seen in the pelvis.

Tumor markers were all negative (CA 19-9: 7.0 U/ml, CEA: 2.0 ng/ml, CA-125: 4.0 U/ml, and AFP: 1.4 ng/ml). A CT scan of the chest and a whole body scan were normal.

Exploratory laparotomy revealed a left ovarian mass measuring 20 × 18 cm, with a normal small uterus, normal right tube and ovary. Pelvic washings were negative for malignant cells. Since the left fallopian tube was adherent to the mass, with no normal ovarian tissue identified, a left salpino-oophrectomy was performed. The frozen section was consistent with a mature cystic teratoma. Pathology reported a 2,390-gram mass measuring 19.5 × 14 × 13 cm with about 6,000 ml of clear fluid, sebum, black hair and a tooth within the cyst. Sections confirmed a mature cystic teratoma with epithelium, adnexal structures, mature glial tissue, peripheral nerve, ganglion, cartilage and Leydig cells. No immature elements were identified. Analysis of the cyst fluid for androgens revealed elevated androstenedione (309 ng/dl) and testosterone (213 ng/dl) (table 1). Repeat androstenedione and testosterone levels on post-operative day 10 dropped precipitously to 93 and 44 ng/dl, respectively.

Due to her significant past medical history, we retrospectively considered a diagnosis of immune-mediated encephalitis to explain the clinical progression of her disease. The recently described entity known as the NMDAR encephalitis, a paraneoplastic syndrome associated with ovarian teratomas, was consistent with her clinical presentation. Serum archived pre-operatively was analyzed for antibodies to NR1/NR2 heteromers of the NMDAR, and immunohistochemistry studies were performed on tumor sections as previously described [1]. Serum anti-NMDAR antibodies were positive with a titer of 1:200. Six months postoperatively, these antibodies were undetectable in the serum. Immunohistochemistry studies showed that the antibodies of the patient reacted with areas of the tumor that had nervous tissue expressing the NMDAR, specifically the obligatory NR1 subunit of the NMDAR (fig. 1). Archived CSF was not available from the time of the encephalitis.

At the 4-month follow-up visit, the patient reported regular menses and a slowing of hair growth since the time of the surgery. She had been seizure-free in the postoperative period and her mood had stabilized. Her androgen levels were normal.

Table 1. Androgen profile of the patient (serum and cyst fluid) pre-operatively and 1 week postoperatively

Androgens	Pre-operatively		Postoperatively (serum)
	serum	cyst fluid	
Androstenedione, ng/dl	305	309	93
Testosterone, ng/dl	187	213	44
17-OHP (hydroxyprogesterone), ng/dl	411	N/A	183
DHEA (dehydroepiandrosterone), ng/dl	958	N/A	39
DHEAS (dehydroepiandrosterone sulfate), μg/dl	42	N/A	22

Normal ranges of serum: androstenedione (37–244 ng/dl), testosterone (0–90 ng/dl), 17-OHP (16–283 ng/dl), DHEA (160–700 ng/dl), DHEAS (33–265 μg/dl). Cyst fluid has no normal range.

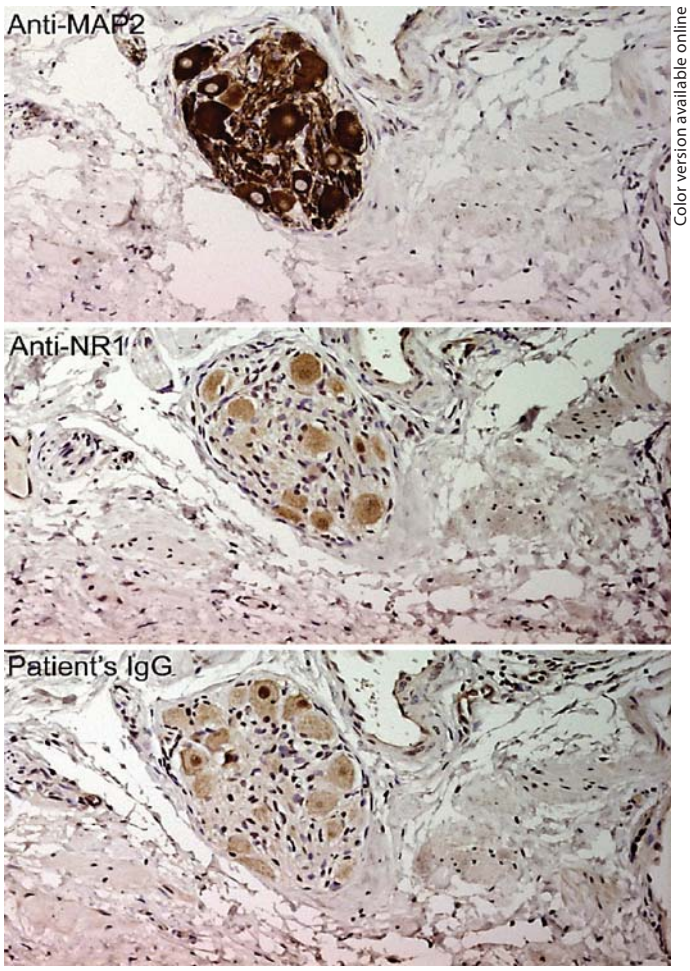

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Fig. 1. Tumor section stained with MAP2 identified the presence of nervous tissue. Consecutive sections show staining of the same area with an antibody against NR1 (an obligatory subunit of NMDA receptors), and with antibodies in the patient's IgG isolated from serum. The techniques and immunoperoxidase method have been reported in Dalmau et al. [1]. Sections counterstained with hematoxylin. ×200.

Discussion

We report on the clinical presentation of a 15-year-old girl who was diagnosed with a virilizing mature cystic ovarian teratoma, which had also caused autoimmune encephalitis 16 months prior to her tumor diagnosis. Individually, these are 2 rare associations with ovarian teratomas, and this is the first report of these uncommon associations occurring in the same patient.

Benign cystic teratomas comprise about 10% of all ovarian cysts [2]. Though most commonly seen in women in the reproductive age group, they can occur at any age. In children and adolescents, mature cystic teratomas or dermoid cysts are the most common forms of ovarian tumor. These tumors generally have a minimal potential for malignant transformation, roughly quoted as 1–2% [2]. In a retrospective review of 134 children and adolescents admitted for ovarian lesions in Melbourne, Australia over an 11-year period, 60.4% were found to have functional or physiological ovarian cysts, 32.8% had neoplastic lesions, and a palpable mass was identified in 53.7% of them. Twenty-seven of the patients had mature cystic teratomas, and 77.8% of these children were under 12 years [3]. There is a recent report of bilateral mature cystic teratomas occurring in a premenarchal girl [4].

Virilization due to ovarian teratoma is extremely rare in the pediatric population. Occasional reports have been published on adult women [5, 6] mostly in the post-menopausal age group. In these patients, the tumor was found to produce high levels of testosterone and androstenedione which promptly regressed after tumor excision, as in our patient. Benign cystic teratomas are also reported to produce β-human chorionic gonadotropin [7], thyroid-

stimulating hormone, estrogen and prolactin [8], but this is rare.

The patient's past medical history of encephalitis of unknown etiology a year prior to the diagnosis of the teratoma led us to consider, in retrospect, the rare entity of immune-mediated encephalitis. One of the earlier described forms of this immunological phenomenon is paraneoplastic limbic encephalitis (PLE). PLE has been known to manifest itself as a constellation of neurologic symptoms primarily affecting the limbic system and the temporal lobes. It is characterized by personality changes, irritability, depression, seizures, memory loss, confusion, and, rarely, dementia in association with a neoplastic disease [9]. The currently accepted hypothesis for the pathogenesis of PLE is an immune-mediated response against the nervous system. Cancers of the lung, gonads, breast, thymus, gastrointestinal tract and genitourinary system as well as Hodgkin's disease may be associated with PLE [9, 10]. Gultekin et al. [9] proposed a set of clinical diagnostic criteria comprised of a compatible clinical picture, an interval of <4 years before the cancer diagnosis, exclusion of other neuro-oncological complications, and at least one of the following: CSF with inflammatory changes but negative cytology, MRI demonstrating temporal lobe abnormalities and an electroencephalogram showing epileptic activity in the temporal lobe.

Most cases of PLE have been described in the adult population [9], though a few cases have been described in children, all of whom were adolescent girls [11–16]. In these reports, PLE was seen in association with immature teratomas. There are only 2 previous reports of PLE in a patient with a mature cystic teratoma [17, 18]. MRI findings in PLE have been noted to be variable, ranging from none to temporal lobe abnormalities or abnormalities in other regions of the brain including the brainstem, hypothalamus, cingulate gyrus and basal frontal lobe [9].

Several auto-antigens have been proposed to be responsible for this immune encephalitis. In the report by Gultekin et al. [9], 60% of the patients with PLE had antineuronal antibodies, including anti-Hu and anti-Ma2. Dalmau et al. [1] have described patients with a new type of treatment-responsive encephalitis and ovarian teratoma, who harbored antibodies in their serum and CSF which were reactive with the NMDAR. In their series, the patients specifically had antibodies to the NR1/NR2 heteromers of the NMDA receptor. These patients also had NMDAR expression on their teratomas, documenting this entity as an onconeural antigen [1]. The 12 patients studied all demonstrated CSF pleocytosis and a clinical presentation similar to that of our patient. Although it was initially suggested that the main epitope was in the NR2 subunit, recent studies indicate antibody reactivity is dependent on the presence of NR1 [19].

Serum archived pre-operatively from our patient was positive for antibodies to the NR1/NR2 heteromers of the NMDAR. Six months postoperatively, these antibodies were undetectable in the serum. Immunohistochemistry performed on tumor sections showed reactivity with a commercially available antibody against NR1 as well as with the antibodies present in the patient's serum. Overall, these findings, along with the initial CSF studies showing inflammatory changes, established the diagnosis of NMDAR encephalitis.

Although this rare association has been increasingly identified and reported, it may often be overlooked due to the complexity of the clinical presentation and the lack of a temporal association between the diagnosis of the encephalitis and an otherwise benign ovarian tumor. This immune phenomenon should also prompt the physician to rule out an ovarian teratoma in a young woman with unexplained encephalitis. Our report is also the first report of a benign cystic teratoma with 2 extremely rare associations, virilization and immune-mediated encephalitis.

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