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Anti-*N*-methyl-D-aspartate receptor limbic encephalitis associated with mature cystic teratoma of the fallopian tube

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Abstract

Anti-*N*-methyl-D-aspartate receptor (NMDAR) limbic encephalitis is the most common form of paraneoplastic encephalitis that is associated with teratomas. Because tumor removal leads to better clinical outcomes, it is essential to reveal the location of the teratomas. This is the first reported case of anti-NMDAR encephalitis associated with teratoma of the fallopian tube. Salpingo-oophorectomy improved neurological symptoms and immunohistochemical examinations indicated the expression of NMDAR on neuroglial cells within the fallopian tube teratoma. Teratomas of the fallopian tube cause anti-NMDAR encephalitis; the imaging analysis and exploratory laparoscopies of the fallopian tube as well as of the ovary should be considered. Surgical removal of both fallopian tubes and ovaries with a normal appearance should be considered for patients in whom immunotherapy is not effective.

Key words: anti-*N*-methyl-D-aspartate receptor, exploratory laparoscopy, fallopian tube teratomalimbic encephalitissalpingo-oophorectomy.

Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) limbic encephalitis is known as one of the most common forms of paraneoplastic encephalitis – particularly in young women – and is frequently associated with ovarian teratoma.[1,2] Surgical removal of the ovarian teratoma with immunotherapy is the first-line treatment; however, these tumors may not be detected in many patients.[3] Patients receiving first-line immunotherapy with tumor removal in the early phase have better clinical outcomes than those receiving the same treatment in the late phase or those who do not undergo tumor removal with first-line immunotherapy.[1–3] Thus, the detection of teratoma is essential for the management of female patients diagnosed or even suspected of having limbic encephalitis.

On the other hand, mature cystic teratomas are the most common form of benign germ cell tumors. Although their extragonadal occurrence has been well documented in regions such as the sacrococcygeal area, retroperitoneal cavity, mediastinum, cranium, and neck, a majority of the teratomas found in women of reproductive age originate from the ovary, and teratomas of the fallopian tube are considered to be rare.[4]

Although most studies have reported that a majority of the teratomas detected in cases of anti-NMDAR limbic encephalitis originate from the ovaries,[1] to our knowledge, our report is the first to document a case of anti-NMDAR limbic encephalitis caused by teratoma of the fallopian tube and to demonstrate the expression of NMDAR in the neurological tissues of fallopian tube teratomas. For patients in whom immunotherapy is not effective and in whom tumors are not identified, removal of the ovary remains controversial but may prove to be effective.[5,6] However, the removal of the fallopian tube in addition to the removal of the ovary has not been discussed.

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Case Report

A 35-year-old woman (gravida 0) with gradually progressive manic state and hallucination-like positive symptoms of schizophrenia and seizures was transferred to a teaching hospital on the 9th day post-onset. Her prior medical history was unremarkable. She was disoriented and showed severe anterograde amnesia. A polycystic mass of 37 × 19 mm in diameter was detected beside the left ovary with high intensity on T2-weighted magnetic resonance imaging (MRI) and low intensity on T1-weighted MRI. In addition, a high-density area of local calcification was detected on computed tomography (CT) images. These findings led to the suspicion of the presence of a teratoma originating from the paraovary or sacrum (Fig. 1). The patient was treated with a high dose of i.v. methylprednisolone (1000 mg/day, 9th–11th days). Her psychological symptoms were slightly improved; however, she continued to require the administration of sedative agents. In the laparoscopy performed on the 17th day post-onset, a solid hydrosalpinx-like mass was identified on her left fallopian tube that prompted a left salpingo-oophorectomy (Fig. 2). The macroscopic findings and intraoperative frozen section indicated that the tumor was mature cystic teratoma of the fallopian tube and that the left ovary was normal. Her ability to engage in conversation gradually improved from the second postoperative day, and schizoid symptoms and memory functions were remarkably improved from the 10th postoperative day. She was transferred to a rehabilitation facility on the 56th postoperative day.

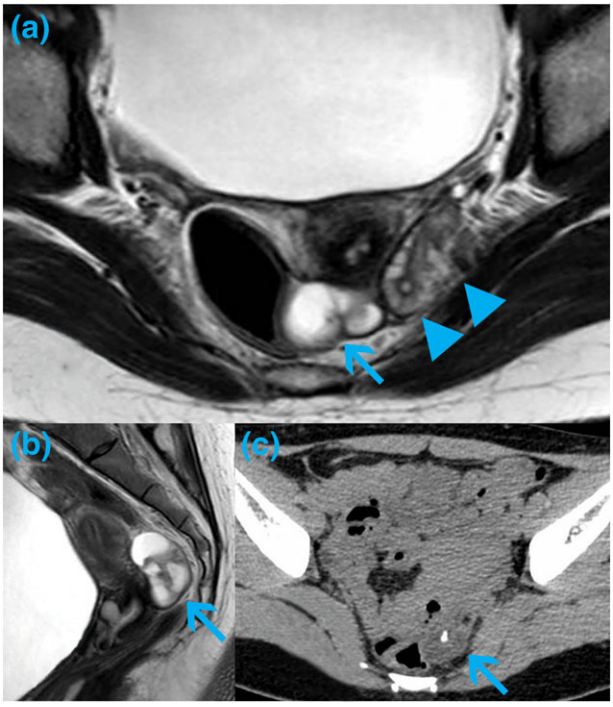

Figure 1 Imaging of teratoma of the fallopian tube. (a) Transverse and (b) sagittal T2-weighted magnetic resonance imaging show the polycystic mass (arrow) beside the ovary (triangle) together with a high-density area of local calcification shown on (c) the computed tomography image.

Anti-NMDAR antibodies were detected in cerebrospinal fluid retrieved on the 9th day post-onset. The diagnosis of mature cystic teratoma was confirmed on histological examination of the epidermal tissue, bone, and cartilage, which revealed the characteristic tumors indicative of mature cystic teratomas. Interestingly, numerous lymphocytes were observed surrounding a mature tissue that resembled the cells found within the cerebral hemispheres, suggesting autoimmune activity of the patient's immune system against her own neuroglial tissues. Subsequently, immunohistochemical examinations were performed using the primary antibodies anti-NR1 (AB9864, Millipore) and anti-NR2A (05-901R, Millipore) to demonstrate positive staining of neuroglial cells within the teratoma (Fig. 3).

Discussion

Teratomas originating from the fallopian tube are considered to be rare because, to date, only 74 cases have been reported.[4] Similar to the case of ovarian teratomas, the smaller size of fallopian tube teratomas often renders them as subclinical and difficult to detect on imaging. Therefore, the initial diagnosis of fallopian tube teratoma is often based on the findings from laparotomy or laparoscopy in many cases.[4] For patients who are infertile, hysterosalpingography showing a swollen fallopian tube has been reported to be an initial opportunity to diagnose fallopian tube teratoma.[7] Although the pathogenesis of fallopian tube teratoma has yet to be completely elucidated,[4] advances in diagnostic imaging coupled with increasing opportunities for receiving medical examinations for infertility or encephalitis may lead to a perceived increase in the cases of this type of tubal tumor.

Based on results from numerous case reports, anti-NMDAR encephalitis has been reported to be more frequent than other known forms of paraneoplastic encephalitis.[1–3] Although anti-NMDAR encephalitis was first reported as paraneoplastic limbic encephalitis in young women with ovarian teratoma, the currently established

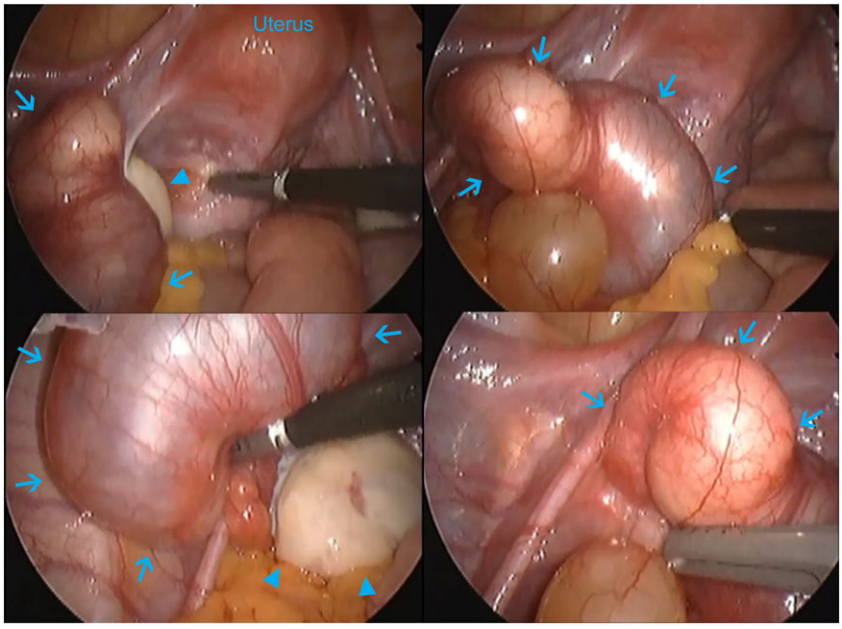

Figure 2 Laparoscopic view of teratoma of the fallopian tube. A solid hydrosalpinx-like mass was identified on the left fallopian tube (arrow), which showed good mobility. The left ovary shows normal findings (triangle).

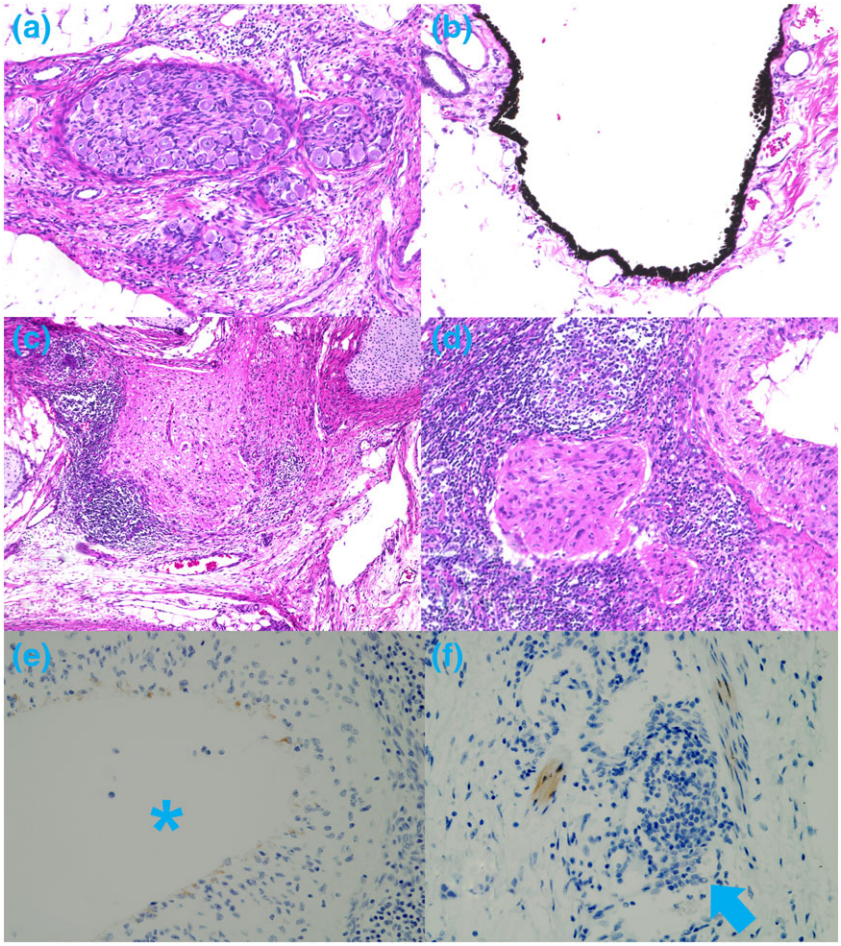

Figure 3 Histological findings of teratoma of the fallopian tube. Hematoxylin–eosin staining shows that this teratoma contained an abundance of neuroglial tissues, such as (a) ganglion, (b) retina, and (c, d) glial cells, surrounded by lymphocytes. Immunohistochemical examinations show that both (e) anti-NR1 and (f) anti-NR2 were positive in neuroglial cells (*) and around lymphoid aggregation (arrow).

test for specific autoantibodies has revealed that not all patients have an underlying tumor.[1,3] In a recently conducted cohort study, 81% of patients with anti-NMDAR encephalitis were women of reproductive age; however, the presence of tumor was only detected in 46% of patients. Furthermore, although only a few cases, such as lung tumor, breast tumor, ovarian carcinoma, thymic carcinoma, and pancreatic cancer, were reported, almost all of the tumors were ovarian teratomas (94%).[2] In contrast to the surgical removal of ovarian teratomas in the early phase, which has been associated with complete recovery or the presence of only mild defects, patients in whom the tumors were not identified have shown poorer responses to immunotherapy and have higher frequencies of severe deficits or death.[3]

Mature teratomas are usually lobulated and cystic, often containing differentiated tissues, such as bone, teeth, hair, adipose tissue, or neurons; the current combination of imaging tests (MRI and CT) have the potential for both qualitative as well as quantitative detection of teratomas. This type of a combination of imaging studies can identify a small space-occupying lesion in the fallopian tube and present multiple components of the lesion suggestive of teratoma. However, the efficacy of exploratory laparoscopies or blind oophorectomies may be effective for patients with anti-NMDAR encephalitis and in whom the tumors have not been identified. For example, some cases have revealed improvements in clinical symptoms following blind oophorectomy.[1,5,8] In those successful cases, the ovarian teratoma was revealed only by pathological examination after the operation[8] or not identified at all.[5] In addition to demonstrating the efficiency of oophorectomy, these case reports indicated that tumor size did not correlate with the encephalitis symptoms.

Although the detection of antibodies in the cerebrospinal fluid is the most reliable evidence for the diagnosis of anti-NMDAR encephalitis,[1,2] histological studies are required for obtaining definitive evidence of the presence of teratoma that plays a role in this encephalitis.[6] In this case, antibodies against the NMDAR NR1 and NR2-A subunits were positive within the neuroglial tissue in the mature cystic teratoma of the fallopian tube, suggesting that an initial sensitization of the lymphocytes may have occurred in the tumor. Reports of immunohistochemical examinations in cases of anti-NMDAR encephalitis are still few in number, and this case is atypical because of the demonstration of neurological tissues in the teratoma itself that directly expressed NMDAR as well as the finding that anti-NMDAR encephalitis was caused by teratomas located in the fallopian tube.

In summary, to our knowledge, this is the first report of anti-NMDAR encephalitis associated with teratomas of the fallopian tube; this report also demonstrated the expression of NMDAR in fallopian tube teratomas on conducting immunohistochemical examinations. We conclude that teratomas of the fallopian tube are rare but may cause anti-NMDAR encephalitis. Removal therapy may also improve functional prognosis; thus, careful imaging analysis and exploratory laparoscopies against sites where teratomas may develop, including the ovaries, is essential. Because of the low frequency associated with the identification of ovarian teratomas in patients with anti-NMDAR encephalitis and the severe outcomes of patients with unrecognized teratomas, surgical removal of both fallopian tubes and ovaries (salpingo-oophorectomy) with normal appearances should be considered for patients with anti-NMDAR encephalitis in whom immunotherapy is ineffective.

Disclosure

The authors have no financial interests to declare in relation to the content of this article.

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