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Case Report

Ovarian teratoma development after anti-NMDA receptor encephalitis treatment

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Abstract

Background: Anti-NMDA-R receptor encephalitis occurs predominantly in younger women and is often comorbid with ovarian teratoma, a feature that is often absent in children. Here, we report our experience with two pediatric patients, in whom no tumors were present during treatment for encephalitis, but in whom ovarian teratomas developed without encephalitis relapse after treatment was completed.

Cases: Patient 1 was a 14-year-old girl who was diagnosed due to characteristic symptoms and anti-NMDA-R antibody. MRI scanning during treatment revealed no ovarian tumors, but a tumor developed in the right ovary 10 months after onset. Another tumor developed in the left ovary 3 years after onset, and a mature ovarian teratoma was confirmed after bilateral partial ovariectomy. Patient 2 was an 11-year old girl who was also diagnosed due to characteristic symptoms and anti-NMDA-R antibody. Imaging during treatment revealed no ovarian tumors, but a 2.5-cm tumor mass was found in the left ovary 10 months after onset, and a mature ovarian teratoma was confirmed after partial ovariectomy.

Discussion: This case report suggests the need for regular tumor screening after treatment for anti-NMDA receptor encephalitis because of potential subsequent tumor development, even in pediatric patients who initially present with no comorbid tumors. No analysis of relapse risk has yet been reported in cases of tumor development after treatment, and at this point, whether or not resection is needed to prevent relapse remains unclear. However, because teratomas usually grow, have an associated risk of torsion, and can be malignant, tumor removal should be considered.

Keywords: Anti-NMDA receptor encephalitis; Ovarian teratoma; Treatment; Children

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1. Introduction

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is an autoimmune NMDA glutamate receptor-mediated encephalitis first proposed by Dalmau et al. in 2007 [1]. The disorder is characterized by psychiatric symptoms, disturbed consciousness, central hypoventilation, involuntary movements, and seizures, and it occurs predominantly in younger women, often comorbid with ovarian teratoma. However, teratoma is often absent in children [2,3]. In patients with teratoma, the tumor usually found at the time of encephalitis diagnosis. We are here reporting our experience with two pediatric patients in which no tumors were present during treatment for encephalitis, but ovarian teratomas developed without encephalitis relapse after treatment had been completed.

This study was approved by the local ethics of Chiba Children's Hospital, and obtained informed consent from patients.

2. Patient reports

2.1. Patient 1

A 14-year-old girl with no history of illness presented with psychotic symptoms, including incomprehensible behavior, auditory hallucinations, and visual hallucinations. Following these symptoms, she experienced abnormal movement including oral dyskinesia and dystonia, and breathing instability, which necessitated treatment in the intensive care unit. Blood analyses were normal, but a CSF study revealed an increased number of cells. Brain MRI on day 9 and pelvic MRI on day 6 and 79 showed normal findings. A cell-based assay using HEK293T cells that express GluN1 & GluN2B on the cell membrane [4] verified the presence autoantibodies in her CSF, leading to a diagnosis of anti-NMDA-R encephalitis. The patient received steroids, immunoglobulin, and plasma exchange therapy; however, this first-line treatment was ineffective. Three months after onset, the patient was administered cyclophosphamide (500 mg/m^2 per month for 3 months), which resulted in a decrease in abnormal movements, and she gradually began to recover. Seven months after onset, she was discharged without any apparent sequelae. MRI scanning during treatment revealed no ovarian tumors, but a tumor that was 13 mm in diameter developed in the right ovary 10 months after onset. At this time, we considered the possibility of recurrence of her symptoms and also considered surgery, but she did not have symptoms due to tumor and was followed up without surgery. Another tumor that was 5 cm in diameter developed in the left ovary 3 years after onset. Although she remained asymptomatic, she was at risk of torsion from the size of the tumor and was judged as indicated for surgery, and a mature ovarian teratoma was confirmed on bilateral partial ovariectomy despite the absence of encephalitis relapse (Figs. 1 and 2).

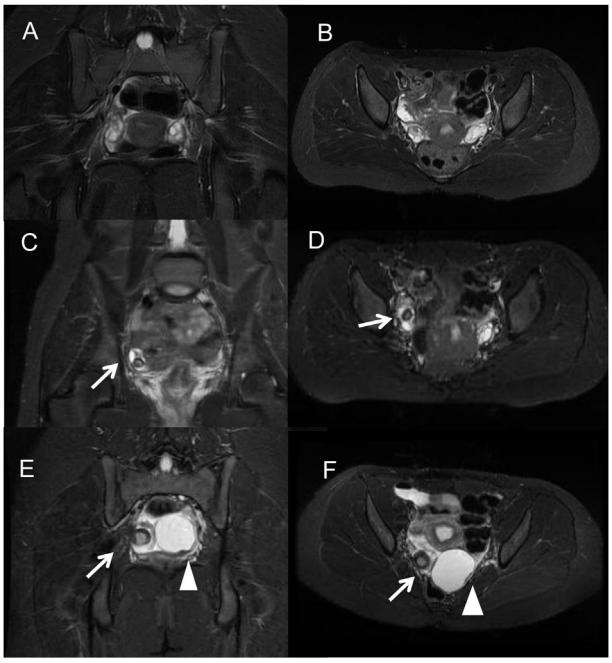

Fig. 1. Patient 1. Pelvic MRI with short-tau inversion recovery (STIR). (A, C, E) are coronal. (B, D, F) are axial. (A, B) MRI showed normal findings at encephalitis onset. (C, D) A tumor (arrow) that measured 13 mm in diameter developed in the right ovary 10 months after onset. (E, F) Another tumor (arrowhead) that measured 5 cm in diameter developed in the left ovary 3 years after encephalitis onset, and was confirmed as a mature ovarian teratoma after bilateral partial ovariectomy.

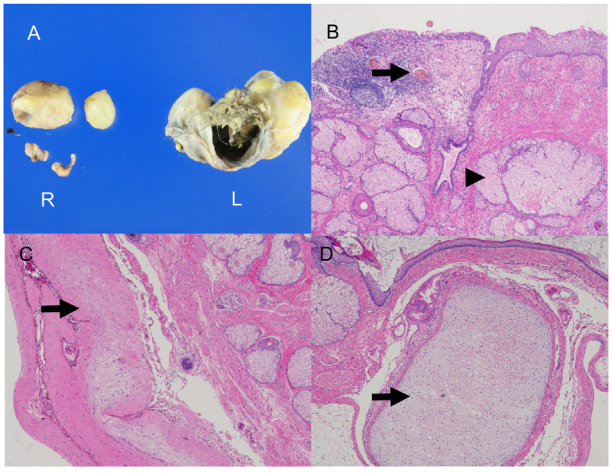

Fig. 2. Patient 1. Mature ovarian teratoma was confirmed after bilateral partial ovariectomy (A–D). (A) Ovarian teratoma with admixture of sebum and hair. (B) Various tissue components of mature teratoma. Sebaceous glands (arrowhead). Hair follicle (arrow). (C) Glial tissue (arrow). (D) Cartilage tissue (arrow). There were no inflammatory changes such as infiltration of lymphocytes.

2.2. Patient 2

An 11-year old girl presented with abnormal speech and behavior, and she was admitted to a different hospital on day 5. Disturbed consciousness and involuntary movements of oral dyskinesia and dystonia worsened despite pulse steroid therapy, and the patient was transferred to our hospital on day 16. Blood analyses were normal, but a CSF study revealed an increased number of cells. Brain MRI on day 18 yielded normal results. Pelvic MRI on day 18 showed normal findings. Indirect immunofluorescence assay using commercial kit (Autoimmune Encephalitis Mosaic 1, Euroimmun, Lübeck, Germany) also verified the presence of autoantibodies in CSF, leading to a diagnosis of anti-NMDA-R encephalitis. The patient responded to cyclophosphamide (500 mg/m^2), which was administered on day 18. After 2 courses of treatment, she was discharged without any apparent sequelae on day 72. Imaging during treatment revealed no ovarian tumors, but a 2.5-cm tumor mass was found in the left ovary 10 months after onset. Despite the absence of encephalitis relapse, a mature ovarian teratoma was confirmed after the partial ovariectomy that was performed 1 year after onset because of intermittent lower left abdominal pain (Figs. 3 and 4).

3. Discussion

This study suggested the need for regular tumor screening after treatment for anti-NMDA receptor encephalitis because of potential subsequent tumor development, even in pediatric patients who initially present with no comorbid tumors.

The incidence of tumor comorbidity varies from study to study. Dalmau et al. reported an incidence of

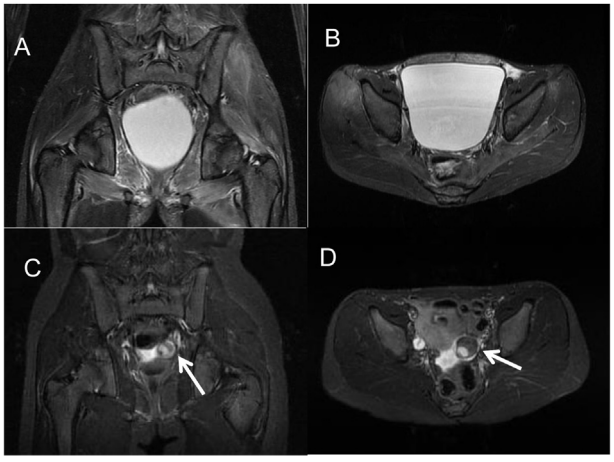

Fig. 3. Patient 2. Pelvic MRI with STIR. (A, C, E) are coronal. (B, D, F) are axial. MRI showed normal findings at encephalitis onset. (C, D) A 2.5-cm tumor mass (arrow) was found in the left ovary 10 months after onset.

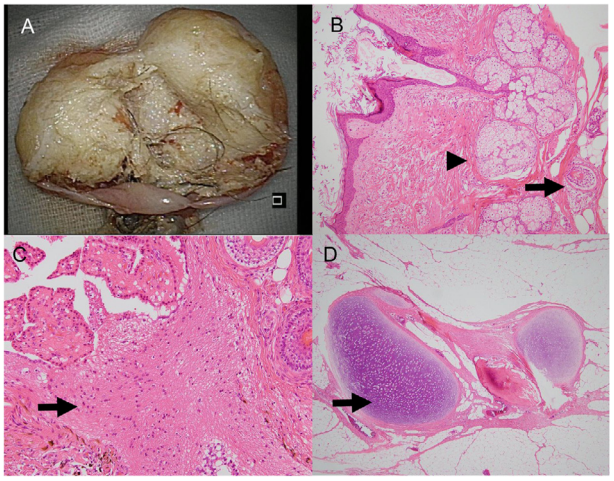

Fig. 4. Patient 2. Mature ovarian teratoma was confirmed after partial ovariectomy (A–D). (A) Ovarian teratoma with admixture of sebum and hair. (B) Various tissue components of mature teratoma. Sebaceous glands (arrowhead). Hair follicle (arrow). (C) Glial tissue (arrow). (D) Cartilage tissue (arrow). There were no inflammatory changes such as infiltration of lymphocytes.

20–25% in 2011 [5]. In a subsequent report by Titulaer et al., tumors were present in 220 out of 577 patients (38%). The tumors were mature teratomas in 211 patients, but were malignant in the remaining 9 patients (4%). The incidence of tumor comorbidity was extremely low in patients younger than 12 years of age, with tumors reported in 4 out of 68 patients (6%), and the frequency was also low in male patients, with tumors reported in 7 out of 109 patients (6%) [2]. Based on these past reports, tumors usually are not present at diagnosis, particularly in pediatric patients, as seen in the two patients in this report.

A search for patients in whom tumors were not present during treatment for encephalitis but who subsequently developed tumors revealed only two reports, one by Armangue et al. [6], in which a patient developed a tumor 1 year after onset of encephalitis, and a report by Horino et al., in which a patient developed a tumor 1 year after onset of encephalitis [7]. Although there is no consideration as to why tumors can be formed later, it is possible that the tumors were too small to be noticed when cases presented encephalitis. Even though this is a very low number of reported cases, both patients developed tumors without any encephalitis relapse after the end of treatment, suggesting the need for continued screening in view of the potential for tumor development after treatment for encephalitis. Considering that both patients reported here developed tumors after 10 months, it seems that screening should be continued for at least 1 year. In comparison, previous reports have recommended a follow-up period of 2 years [4] and 4 years [6], and Titulaer et al. suggest that, in female patients aged 12 years or older, a screening approach similar to that of paraneoplastic syndrome is

required (MRI of the abdomen and pelvis every 6 months for 4 years) [2]. However, the need for repeat screening in young children and male patients is unclear [2]. Further study will be necessary in the future in children.

According to the treatment strategy proposed by Dalmau, tumorectomy is recommended as first-line treatment in patients with tumors during treatment for encephalitis [5]. However, because of the extremely low number of reports, no recommendations can be made as to whether or not tumors should be immediately removed when an ovarian teratoma develops after treatment for encephalitis. The risk of encephalitis relapse must be given priority in considering treatment strategies when a tumor develops after treatment for encephalitis. In assessments of the risk of encephalitis relapse available to date, Titulaer et al. reported an overall rate of 12% [2]. Dalmau et al. reported rates of 20–25%, and the rate of relapse in cases of early tumor removal in patients in the acute phase was significantly lower compared to that in remaining patients or patients without tumors [5,8]. Gabilondo et al. reported a relapse rate of 24% in 2011, and they reported that symptoms of recurrence are milder than those during the first episode [9]. However, no analysis of relapse risk has yet been reported in cases of tumor development after treatment, and at this point, whether or not resection is needed to prevent relapse remains unclear.

Because teratomas usually become larger, carry risk of torsion, and can, although rarely, be malignant, tumor removal should be considered not only for the prevention of relapse. Whether or not aggressive removal is indicated in the small number of patients who develop tumors after treatment for encephalitis requires further study as more cases are reported in the future.

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