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Case Report

Low-Grade Glioma within Mature Cystic Teratoma in a Patient with Anti-N-Methyl-D-Aspartate Receptor Encephalitis: A Case Report

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Keywords

Mature cystic teratoma · Malignant transformation · Low-grade glioma · Anti-NMDAR encephalitis

Abstract

Introduction: Mature cystic teratoma (MCT) is a common type of ovarian tumors that can, in rare cases, undergo malignant transformation. It has been discovered that MCT patients may experience psychiatric symptoms due to the presence of anti-N-methyl-D-aspartate receptor (NMDAR) antibodies, which is the underlying cause of autoimmune encephalitis. Here, we present the first documented case of a patient with anti-NMDAR encephalitis who also had a morphology of low-grade glioma within MCT. ***Case Report:*** A 45-year-old woman presented with seizures, altered consciousness, abnormal NMDAR antibody IgG titers, and abnormal brain MRI findings confirm the diagnosis of anti-NMDAR encephalitis. Physical examination revealed an oval mixed echo mass measuring 54 × 37 mm in the left adnexal area on ultrasound of the uterine appendage. The patient underwent laparoscopic left ovarian and fallopian tube resection. The pathological gross examination revealed a pile of grayish-red cystic and solid fragmented tissue measuring 7 × 6 × 2.2 cm. Histological examination revealed characteristic components of MCT. Furthermore, the solid component of the gross tissue showed proliferative and densely arranged astrocytes with cellular atypia, which were positive for GFAP and Olig-2, negative for IDH1 and EMA. And the Ki67 index was approximately 10%, suggesting the presence of low-grade glioma lesions. The patient was diagnosed with malignant transformation of MCT into a morphology of low-grade glioma, not otherwise specified.

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After the removal of the ovarian tumor, the patient's psychiatric symptoms improved. ***Conclusions:*** Low-grade glioma within MCT is a rare occurrence, and the presence of this malignant transformation in patients with anti-NMDAR encephalitis is even more uncommon.

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Introduction

Mature cystic teratoma (MCT) is the most prevalent benign ovarian germ cell tumor in women of reproductive age [1]. Ectodermal tissues and sebaceous material are frequently observed in almost all cases. In certain instances, well-differentiated neuroectodermal tissue, such as astrocytes, ependyma, and oligodendrocyte components, may be present within MCT [2]. Although most MCTs are typically considered benign, there is a rare phenomenon, estimated to occur in approximately 2% of cases, in which they can undergo malignant transformation [3]. All components within a teratoma have the potential to undergo malignant transformation, and various histological types of malignant transformation have been reported, including squamous cell carcinoma, adenocarcinoma, sarcoma, malignant melanoma, and others. And it is worth noting that occurrence of central nervous system (CNS) tumors, such as astrocytoma, glioblastoma, and ependymoma, arising in MCT is exceptionally rare, with only a few individual cases reported so far [4, 5]. Furthermore, it is crucial to emphasize that in certain cases, patients with MCT may experience psychiatric symptoms, memory deficits, hypoventilation, and decreased consciousness [6]. These symptoms have been attributed to specific autoantibodies that target the N-methyl-D-aspartate receptor (NMDAR), resulting in an attack on NMDA-type glutamate receptors at central neuronal synapses. This autoimmune response is responsible for the prominent psychiatric and behavioral symptoms observed in these patients and serves as the underlying cause of autoimmune encephalitis [7]. Studies have provided evidence indicating that MCT of the ovary is a significant cause of anti-NMDAR encephalitis. In a study involving 501 patients with anti-NMDAR encephalitis, 38% of them were found to have tumors, with 94% of these tumors being ovarian teratomas (OTs) and 2% being extraovarian teratomas [8]. This evidence strongly supports the association between anti-NMDAR encephalitis and OT, highlighting the importance of recognizing this connection.

This paper presents a remarkable case of a low-grade glioma morphology within MCT in a patient with anti-NMDAR encephalitis. This case represents the first documented instance of such a transformation, emphasizing the rarity of this event and its correlation with anti-NMDAR encephalitis.

Case Report

A 45-year-old female patient presented with seizures, altered consciousness, incoherent speech, irritability, and urinary incontinence for a month. The brain magnetic resonance imaging (MRI) of the patient revealed the presence of multiple patchy and punctate hyperintense signals in the bilateral frontal lobes, left insular lobe, and left basal ganglia on both T1-weighted and T2-weighted MRI sequences. The T2 FLAIR sequence demonstrated high signal intensity, but no enhancement was observed (as shown in Fig. 1). The laboratory tests revealed that the patient had a NMDAR antibody IgG titer of 1:300 in peripheral blood and 1:100 in cerebrospinal fluid. Additionally, the CA19-9 level was elevated at 48.44 U/mL, while

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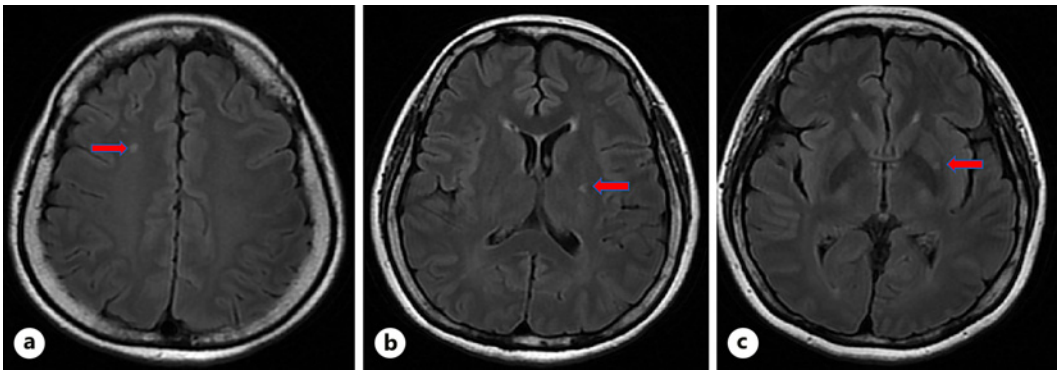

Fig. 1. Brain MRI of the patient revealed the presence of multiple patchy and punctate hyperintense signals (bold red arrow) in the bilateral frontal lobes (**a**), left insular lobe (**b**), and left basal ganglia (**c**).

the CA125 level was within the normal range at 21.9 U/mL. Due to the detection of abnormal NMDAR antibody IgG titers in both peripheral blood and cerebrospinal fluid, abnormal brain MRI findings, as well as symptoms of epilepsy, cognitive impairment, and speech disorders, the patient was ultimately diagnosed with anti-NMDAR encephalitis based on diagnostic criteria [9]. Given the strong association between this disease and teratoma, a bedside ovarian ultrasound imaging examination was performed. The result revealed an oval mixed echo group measuring 54 × 37 mm in the adnexal area. The lesion exhibited clear boundary, a thin cyst wall, and homogeneous, dense, punctate hyperechoic areas, as well as liquid anechoic areas within. These findings suggest a possible teratoma in the left adnexal area. No lesions were detected in the peritoneum on ultrasound examination.

The pathological gross examination (shown in Fig. 2a) revealed a pile of grayish-red fragmented tissue measuring 7 × 6 × 2.2 cm. Some of the tissue fragments were cystic, with a wall thickness ranging from approximately 0.1 to 0.8 cm. Two solid tissues with diameters of 1.3 cm and 1.8 cm were observed. The solid area appeared grayish white with a medium texture; no obvious hair was detected. Microscopic examination found that ectodermal components epidermis, skin appendages and mesodermal component mature adipose tissue were easily found (shown in Fig. 2b). Other mesodermal and endodermal derivative components were also found, such as bone tissue, mature cartilage tissue, respiratory epithelium tissue, and salivary gland tissue (shown in Fig. 2c). No mature or immature neural components were identified. These findings confirm the pathological diagnosis of MCT. Furthermore, the solid component of the gross tissue displayed histological features characterized by a significant proliferation of densely arranged astrocytes, exhibiting sparse cytoplasm and mild to moderate atypia (shown in Fig. 3a). There were variations in cell density, with some regions showing abundant cells and others showing sparse cellularity (shown in Fig. 3b). The surface was lined with ciliated columnar epithelium; beneath the epithelium, a neurofibroid-like matrix was present (shown in Fig. 3c). Mitotic figures are rare, and there is a small amount of blood vessels and lymphocytes in the interstitium, with no necrosis observed. We think that the morphology, particularly the presence of a relatively large glial cell proliferation area measuring approximately 1.3 cm, densely arranged cells with cellular atypia (shown in Fig. 3d), the absence of significant necrosis, strongly suggests a diagnosis of a low-grade glioma.

Immunohistochemistry analysis of the solid area (shown in Fig. 4) revealed diffuse and strongly positive cytoplasmic staining of GFAP, confirming its glial origin. The negative expression of EMA suggests the exclusion of ependymal origin, further supporting astrocytic origin. Olig-2 showed partial positivity, indicating the presence of oligodendroglial

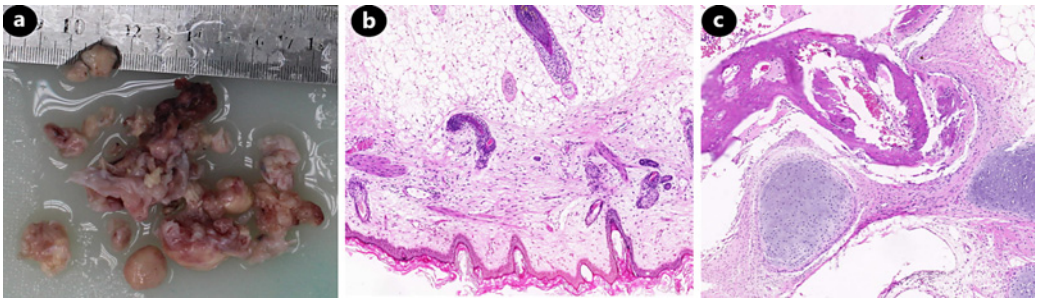

Fig. 2. a Pathological gross examination of the tumor. The tumor exhibited a mass of fragmented cystic and solid tissue, with a grayish-red color. Its dimensions were measured to be 7 × 6 × 2.2 cm. **b**, **c** Histological examination of the cystic tissue of the tumor. Cystic area displayed epidermis, skin appendages, and mature adipose components at low magnification. H&E stain. ×100.

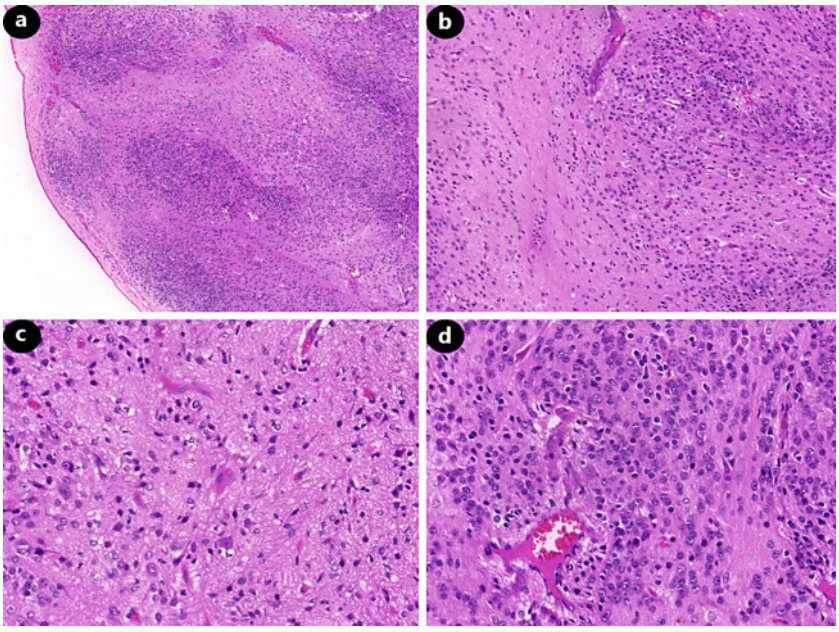

Fig. 3. Histological examination of the solid tissue of the tumor. **a** Proliferative and densely arranged astrocytes. H&E stain. ×100. **b** Variations in cell density, with some regions showing abundant cells and others showing sparse cellularity. H&E stain. ×200. **c** Neurofibroid-like matrix was present. H&E stain. ×400. **d** At higher magnification, the low-grade glioma component exhibited interweaving cell proliferation with crowded and chromatin-rich nuclei, displaying atypia. H&E stain. ×400.

components. P53 and IDH1 R132H were negative. The Ki67 index was approximately 10% positive expression, suggesting the presence of low-grade glioma lesions [10]. However, further molecular studies are required to confirm the diagnosis according to the 2021 WHO classification of the CNS tumors, which are unable to conduct in our institution.

Based on these findings, the patient was diagnosed with malignant transformation of MCT into a morphology of low-grade glioma, not otherwise specified. The patient underwent laparoscopic resection of the left ovary and fallopian tube without any additional treatment for ovarian tumors. Peritoneal resection was not performed, and there is no history of peritoneal glioma. The patient was treated with immunosuppression and hormone therapy. A

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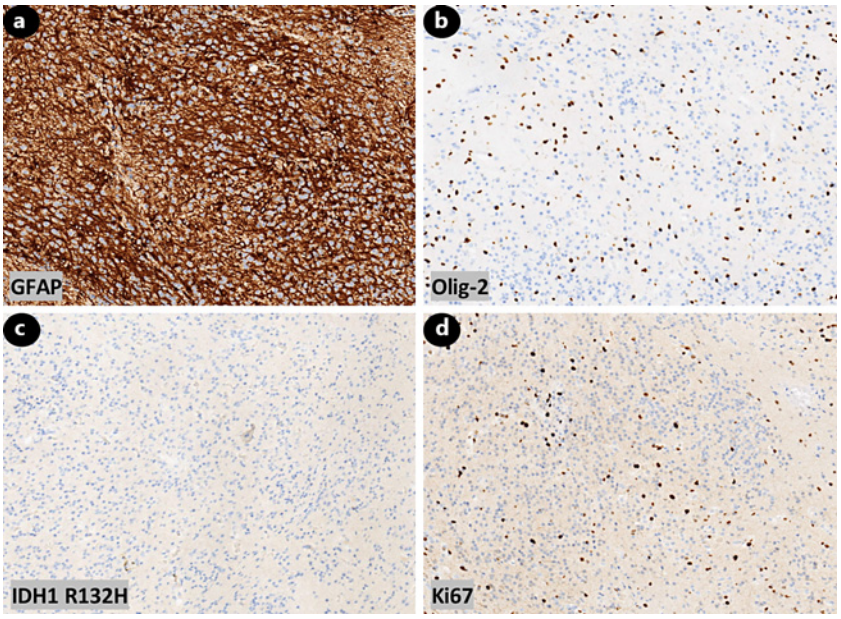

Fig. 4. Immunostaining of the solid components. **a** GFAP showed strong positive staining. H&E stain. ×200. **b** Olig-2 showed partial positivity. H&E stain. ×200. **c** IDH1 showed negative. H&E stain. ×200. **d** The Ki67 index was elevated, with approximately 10% positive expression. H&E stain. ×200.

pelvic CT examination conducted 5 months after tumor resection showed no signs of teratoma recurrence. At the 6-month follow-up, the patient did not exhibit symptoms of seizures or altered consciousness but reported feeling slightly depressed and dreamy. The patient continued taking antipsychotic medication and received regular reviews.

Discussion

Teratoma with malignant transformation refers to the presence of accompanying or secondary malignant tumors within MCT. It is important to note that this category of tumors does not include malignancies associated with monodermal teratoma, such as thyroid cancer, thyroid carcinoid tumors, and neuroectodermal tumors. The diagnosis of malignant transformation in teratoma involves identifying the presence of MCT components along with the evidence of malignant transformation. Malignant transformation can occur in all embryonic tissues present in MCT, with the epithelial components of the ectoderm being more prone to malignancy. Squamous cell carcinoma is the most prevalent type of malignant transformation, comprising 75–85% of cases. Adenocarcinoma is the second most common type, while carcinoids, mucoepidermoid carcinoma, and basal cell carcinoma are rare occurrences. Malignant transformation in astrocytic glioma is extremely uncommon [3, 11]. Primary neuroectodermal tumors of the ovary are monodermal teratoma. There have been only a few reports of glioblastic and neuronal tumors associated or secondary to multiple embryonic teratomas. These rare tumors bear similarities to neuroectodermal tumors found in the CNS [12–14]. Despite their morphologic similarity, primary ovarian astrocytomas do not exhibit the canonical IDH1 R132H mutations seen in CNS diffuse astrocytomas. Ovarian glial and neuronal tumors can be extensively debulked and often completely resected through surgical intervention, whereas this is not typically feasible in the CNS. This difference in surgical management is likely a significant factor contributing to the disparity in recurrence-free and

overall survival rates observed between patients with CNS tumors and ovarian tumors. The mechanism underlying the malignant transformation of MCT remains unclear. Some researchers propose that the prolonged existence of a mature teratoma may play a role in its malignant transformation. Furthermore, age has been identified as a risk factor for the malignant transformation of MCT [15]. Pathological examination reveals that tumors with malignant transformation often have a larger size, but it is important to note that smaller tumors can still undergo malignant transformation. Preoperative diagnosis can be challenging due to the limited number of cases and the absence of specific symptoms and signs.

The case we present exhibits typical pathological characteristics of MCT with a low-grade glioma component in the solid area. A careful gross examination is important when handling specimens of OT with solid areas. Extensive tissue sampling of any solid areas is likely to reveal morphologic features that have significant diagnostic and prognostic value, especially immature elements. Microscopically, the low-grade glioma component exhibited moderately increased cellularity, low to moderate nuclear atypia, and very rare mitotic figures. There was no evidence of vascular proliferation or necrosis. Immunophenotyping results showed no IDH1 R132H mutations. However, further molecular detections are required to confirm the integrated diagnosis according to the 2021 WHO classification of the CNS tumors [16], which are unable to conduct in our institution. The differential histologic diagnosis includes non-neoplastic lesions, such as glial component and reactive glial proliferation. Neither of these conditions exhibit a significant increase in cell density as observed in this case, where interweaving cell proliferation with densely packed nuclei that appeared chromatin rich, displaying atypia, is evident. Additionally, the Ki67 index in both non-neoplastic lesions are typically not higher than 5%, whereas in this case, the Ki67 index is 10%, further supporting the presence of a tumor lesion.

Interestingly, the patient also presented with anti-NMDAR encephalitis, which has not been extensively reported in the current literature. Anti-NMDAR encephalitis is the most common form of autoimmune encephalitis mediated by NMDAR antibodies. Tumors, particularly OT, with a reported penetrance of 94%, have been identified as significant triggers of anti-NMDAR encephalitis [17]. A systematic review of 432 case reports of anti-NMDAR encephalitis demonstrated that out of 293 female patients, 68 (23%) were diagnosed with teratoma [8]. The pathogenesis of anti-NMDAR encephalitis associated with teratoma is possibly due to the presence of nervous tissues in OT. Chefdeville et al. [18] discovered that nervous tissue was present in 96% of anti-NMDAR encephalitis-associated OT, whereas only 38% of control MCTs contained nervous tissue. Teratoma consists of various components, including aggregates of glial tissue, glial tissue itself, lymphoid follicles, as well as irregularly shaped cells and megakaryocytic neurons. The expression of antigens by heterotypic neurons, along with sustained autoimmune damage to neurons, triggers or perpetuates immune responses within the glial tissue. NMDAR autoantibodies are generated by active germinal centers present in the tertiary lymphoid structures and traditional secondary lymphoid organs within teratomas [19]. Eventually, these anti-NMDAR autoantibodies produced by immune cells reach the CNS and cross the blood-brain barrier into cerebrospinal fluid, leading to antibody-mediated neuronal damage [17]. In OT-associated anti-NMDAR encephalitis, the presence of lymphocyte aggregation within or around the neuroglial tissues is a characteristic feature. These lymphocytes are composed of segregated B and T cells and can sometimes form organized structures known as reactive tertiary lymphoid structures [20]. In our case, we observed the lymphocyte infiltrations around the low-grade glioma components in our case, as well as scattered lymphocytes within the solid astrocytoma components. More cases need to be accumulated to further elucidate the underlying mechanism and establish a clear relationship between malignant transformation and the development of anti-NMDAR encephalitis in OT. While our observation suggests potential immune involvement, more

research is necessary to fully understand the implications of these findings. This case report serves as a valuable contribution to the existing knowledge, but additional investigations and accumulation of more cases are required to provide a comprehensive understanding of this complex relationship.

The most effective treatment for patients with combined OT and anti-NMDAR encephalitis is early tumor resection to remove the root cause and block the synthesis of antigens produced by OT. In cases of OT-associated anti-NMDAR encephalitis, the initial symptoms are primarily psychiatric, but neurological symptoms can also be present. In our case, the patient had positive NMDAR antibody IgG in both peripheral blood and cerebrospinal fluid, leading to a diagnosis of anti-NMDAR encephalitis. After the removal of the ovarian tumor, the patient's psychiatric symptoms improved. It is recommended to screen for OT in all patients with anti-NMDAR encephalitis using pelvic and abdominal MRI, as well as abdominal or transvaginal ultrasound, to detect, diagnose, and treat them early.

Conclusions

The aim of reporting this case is to contribute clinical and pathological information regarding the malignant transformation of MCT into a morphology low-grade glioma in the context of anti-NMDAR encephalitis. This case report can potentially enhance our understanding of these rare associations and provide valuable insights for future clinical management. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535708).

Statement of Ethics

This study has been granted an exemption from requiring ethics approval by the Ethical Committee of the Institute Research Ethics Committee of the Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, PR China. This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Wenwen Luo and Jinyue Zheng conceived and designed the study. Wenwen Luo and Bojin Su drafted the manuscript and searched and reviewed the literatures. All authors contributed to the article and approved the submitted version.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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