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CASE REPORT

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Immunotherapy in young adults with mature cystic ovarian Teratoma-Derived squamous cell carcinoma: a case series

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Abstract

Background Mature cystic teratomas (MCTs), also known as dermoid cysts, are common benign germ cell tumors. These predominantly benign tumors can become malignant, particularly in postmenopausal women; the overall transformation rate of MCTs is 1-2%, accounting for approximately 80% squamous cell carcinoma of cases. Malignant transformation remains exceptionally rare in young adults.

Case presentation Herein, we report two cases of squamous cell carcinoma arising from MCTs in a 25-year-old patient, staged FIGO 2018 IIIA1 and IC2 according to the International Federation of Gynecology and Obstetrics (FIGO) 2018 classification. The results of histopathological examination confirmed squamous cell carcinoma arising from the teratomas. Immunohistochemical staining revealed programmed death-ligand 1 expression. Both patients underwent fertility-sparing surgeries and subsequently received adjuvant chemotherapy in combination with programmed death receptor 1 (PD-1) inhibitor immunotherapy. A complete clinical response was ultimately achieved. Patients 1 and 2 were monitored for 29 and 20 months after operation, respectively. A complete response was maintained in Patients1 and 2 for 14 and 16 months, respectively, as of the last follow-up.

Conclusion Squamous cell carcinoma arising from MCTs is exceedingly rare in young adults and exhibits nonspecific clinical manifestations and imaging characteristics, hindering preoperative diagnosis. These tumors display highly aggressive biological behavior and are typically associated with a poor prognosis and a high postoperative recurrence rate. Immunotherapy intervention at diverse different time points for patients at different stages can increase their survival period.

Keywords Malignant transformation of mature teratomas, Squamous cell carcinogenesis, Operation, Chemotherapy, Immunotherapy

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Background

Mature teratomas, a common type of benign ovarian germ cell tumors, are typically composed of tissues derived from two or three germ layers. The malignant transformation rate of mature teratomas ranges from 0.5 to 2% [1], with the incidence being higher in postmenopausal women and being relatively rare in young adults [2]. Squamous cell carcinoma is the most prevalent histopathological type among the cases of malignant transformation of mature teratoma, followed by adenocarcinoma, sarcoma, and melanoma [3]. Surgical resection is the primary treatment modality for this condition. However, innovative therapeutic strategies targeting high-frequency molecular markers are urgently required to improve clinical patient outcomes given the limited efficacy of conventional chemotherapeutic regimens. Immunotherapy has recently demonstrated remarkable efficacy in the treatment of various solid tumors. However, applications of immunotherapy for the treatment of malignant germ cell tumors remain relatively under-reported. This article details two cases of young adults at different clinical stages of squamous cell carcinoma. A complete response was achieved in both patients after postoperative treatment with a combination of chemotherapy and immunotherapy. These results offer valuable insights for the clinical management of these patients.

Case report

Patient 1: A 25-year-old nulliparous woman presented with a one-month history of acutely exacerbated and progressive abdominal distension in the prior 24 h. The medical history was unremarkable for previous ovarian surgery or familial predisposition of malignancy. Pelvic magnetic resonance imaging (MRI) demonstrated a complex cystic and solid lesion measuring $13.0 \times 13.8 \times 21.1$ cm in the pelvic cavity, exhibiting radiological features consistent with the malignant progression of ovarian teratoma (Fig. 1). The results of the evaluation of serum tumor markers revealed substantially elevated CA19-9 (166 U/mL; normal range: 0–37 U/mL) and CA125 (132 U/mL; normal range: 0–35 U/mL) levels. Histopathological examination of frozen intraoperative sections revealed a poorly differentiated carcinoma arising within a malignant teratoma. A comprehensive fertility-sparing surgical approach was adopted given patient age and a strong desire to preserve fertility. The surgical procedures included exploratory laparotomy with right salpingo-oophorectomy; systematic pelvic and para-aortic lymphadenectomy (extending to the level of the renal veins, with the largest lymph node measuring approximately $10 \times 5 \times 4$ cm); multiple peritoneal biopsies; resection of tumor implants from the sigmoid colon surface, right pelvic wall, and right ureter; omentectomy; and left ovarian cystectomy. Cytoreduction was optimal, resulting in R0 resection. The results of postoperative histopathological examination confirmed the presence of a right ovarian somatic neoplasm arising from a teratoma, specifically moderately to poorly differentiated squamous cell carcinoma, with evidence of vascular tumor thrombus. Metastatic carcinoma was identified in the fallopian tube, sigmoid colon serosa, and para-aortic lymph nodes, whereas no tumor infiltration was observed in the remaining resected tissues. Immunohistochemical analysis revealed the following profile: CK5/6 (+), CK7 (-), CK8/18 (focally +), p40 (+), p63 (+), HMB45/Melanoma (-), Ki-67 (80%), S-100 (-), vimentin (+), HER-2 (0), and mutant-type p53 expression. The tumor proportion score (TPS) was 20–30% according to programmed death-ligand 1 (PD-L1) testing (Fig. 2). The clinical staging of this patient was as follows: somatic neoplasms arising from teratomas (squamous cell carcinoma, moderately to poorly differentiated), staged as FIGO 2018 IIIA1. Next-generation sequencing (NGS) analysis identified *PIK3CA*, *TP53*, *KEAP1*, *RRM1*, *RAD54L*, *PDCD1LG2*, and *CD274*

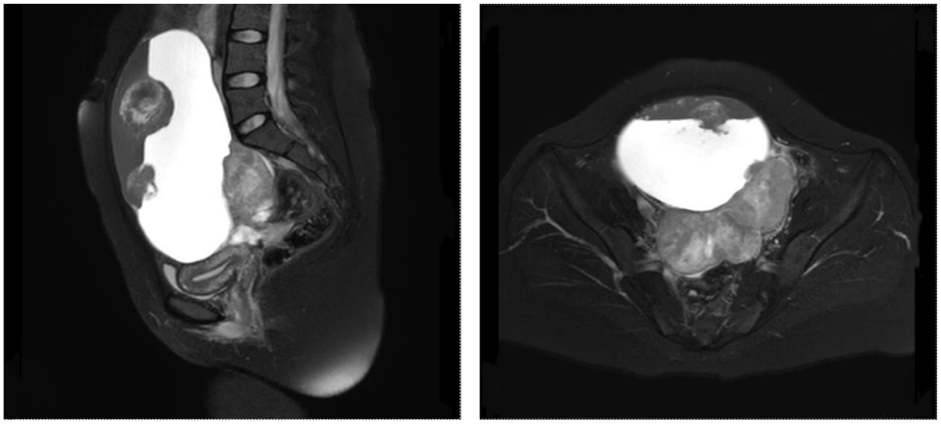

Fig. 1 Magnetic resonance imaging (MRI) of Patient 1 reveals a large ovarian mass measuring approximately $13.0 \times 13.8 \times 21.1$ cm, with imaging characteristics consistent with malignant transformation of a mature cystic teratoma

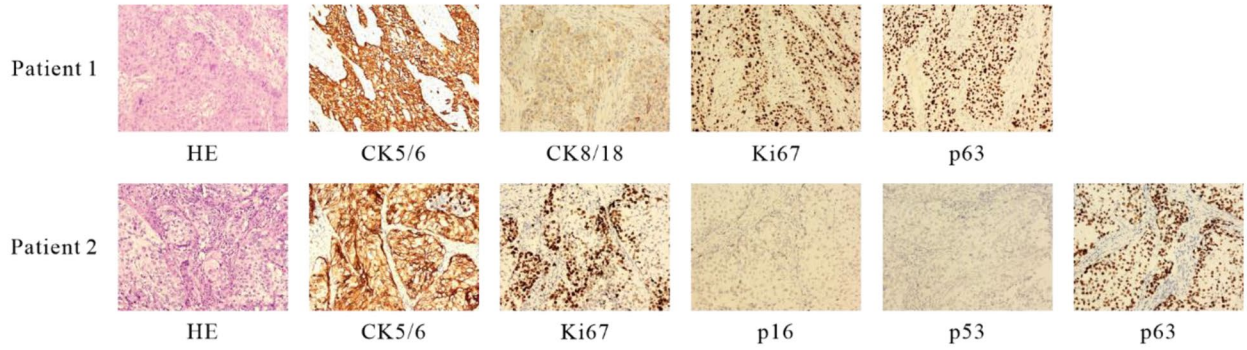

Fig. 2 Histological features of SCC transformation in MCTs from a retrospective chart review

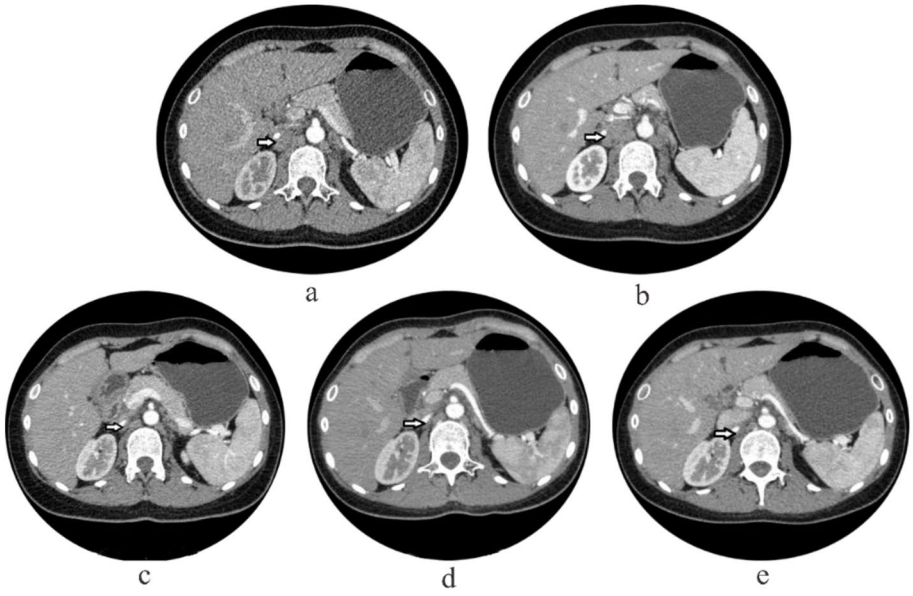

Fig. 3 Abdominal computed tomography (CT) findings of para-aortic lymphadenopathy. (a-b) CT images demonstrate enlarged para-aortic lymph nodes (arrows), showing progressive enlargement. (c-e) Follow-up axial CT images show significant reduction in lymph node size (arrows) after treatment

mutations, wild-type *BRCA1/2* status, and microsatellite stable (*MSS*). The postoperative treatment course of the patient comprised multiple therapeutic phases. Initially, four cycles of standard TC chemotherapy (paclitaxel 175 mg/m² day 1 + carboplatin AUC 5 day 2, q3w) were administered. Postchemotherapy imaging surveillance revealed disease progression, characterized by enlarged para-aortic lymph nodes (3.0 × 1.4 cm; Fig. 3-a) and a new right peritoneal nodule (1.0 × 0.8 cm), prompting therapy intensification. Subsequent treatment involved four cycles of TC chemotherapy combined with bevacizumab (15 mg/kg, q3w). However, follow-up imaging demonstrated disease progression, with para-aortic lymph nodes enlarging to 4.0 × 2.0 cm (Fig. 3-b) and the peritoneal nodule increasing to 3.1 × 2.8 cm. The therapeutic strategy was modified to a BEP regimen (cisplatin 20 mg/m² days 1–5 + etoposide 100 mg/m² days 1–5, q3w + bleomycin 30 mg weekly i.m.) in combination with bevacizumab (15 mg/kg, q3w) and sintilimab (200 mg, q3w) following a multidisciplinary team (MDT) review and consideration of the PD-L1 immunohistochemistry results (TPS 20–30%). The therapeutic response was remarkable following four cycles of this regimen, as evidenced by the complete resolution of the peritoneal nodule and reduction in the para-aortic lymph nodes to 1 × 1 cm (Fig. 3-c), representing a partial response according to RECIST 1.1. Consolidation therapy included two additional cycles of bevacizumab-sintilimab combination therapy, followed by four cycles of sintilimab monotherapy as maintenance treatment. A complete radiological response, confirmed by the final imaging assessment (Fig. 3d/e), was observed. This response was maintained for 14 months with ongoing PD-1 inhibitor therapy, and there was no evidence of tumor recurrence. Additionally,

the patient postoperatively received six cycles of gonadotropin-releasing hormone agonist (GnRH-a) therapy to preserve ovarian function, with menstruation resuming five months after the discontinuation of the medication.

Patient 2: A 25-year-old nulliparous woman presented to our tertiary care center with an pelvic mass incidentally detected during a routine gynecological examination three days prior to admission. Their medical history was unremarkable, with no previous ovarian surgery or family history of malignancies. The results of pelvic MRI demonstrated a large pelvic-space-occupying lesion measuring 17.5 × 10.5 × 22 cm, exhibiting radiological characteristics consistent with those of teratoma with potential malignant transformation. Serum tumor marker evaluation revealed highly elevated levels of CA 19 – 9 (477 U/mL; normal range: 0–37 U/mL) and CA 125 (122 U/mL; normal range: 0–35 U/mL). The results of the histopathological analysis of frozen intraoperative sections confirmed the presence of somatic neoplasms arising from the teratomas. A fertility-sparing surgical approach, specifically right salpingo-oophorectomy, was employed given patient age and the strong desire to preserve fertility. Immunohistochemical analysis revealed the following profile: CK7 (-)、CK5/6 (+), CK20 (-), ER (-), Ki-67 (50%), p63 (+), p40 (+), p16 (-), p53 (-), PR (-), and PD-L1 with a combined positive score of 40 (Fig. 3). The final histopathological diagnosis was a somatic neoplasm arising from teratomas (poorly differentiated squamous cell carcinomas). The tumor was classified as FIGO 2018 IC2 because of the involvement of the surface of the right ovary. NGS genetic testing revealed the following findings: *HRD* positivity, a tumor mutation burden of 15.95 mutations/Mb, *MSS*, and a decreased *PTEN* copy number. Mutations were identified in *ARID1B*, *ATRX*, *HDAC2*, *JAK2*, *KMT2A*, *MTOR*, *PDGFRB*, *PIK3C2B*, *PREX2*, *PTPRD*, *PTCH1*, *SLX4*, *TET2*, and *TSC1*. No mutations were detected in *BRCA1/2*, *K-ras*, or *EGFR*, and no germline mutations were identified. The postoperative treatment course of the patient was systematically divided into sequential therapeutic phases. One cycle of the TC chemotherapy regimen (paclitaxel 175 mg/m² on day 1 + carboplatin AUC 5 on day 2, q3w) was initially administered. A combined therapeutic approach was then initiated following an in-depth MDT discussion and based on the PD-L1 immunohistochemistry results, consisting of a TC regimen alongside sintilimab (200 mg, q3w) for two cycles. This regimen was subsequently changed to sintilimab monotherapy as a maintenance strategy. The results of imaging evaluations confirmed a complete response, and the patient was maintained on PD-1 inhibitor therapy, with the complete response being sustained without evidence of tumor recurrence for 16 months. Additionally, the patient postoperatively received three cycles of GnRH-a therapy to preserve ovarian function, with menstruation resuming three months after the discontinuation of the medication.

Discussion and conclusions

The malignant transformation of mature ovarian teratomas is relatively rare in young adults, and the underlying pathogenesis is not completely understood. Several high-risk factors associated with this condition have been identified, including advanced age, large tumors, rapid tumor growth, and HPV infection [4]. The most frequently mutated genes are *TP53*, *PIK3CA*, *TERT*, and *CDKN2A* among patients experiencing the malignant transformation of teratomas [5–7]. Tamura et al. discovered that most MCT-SCCs (87.5%, 7/8) harbor at least one known oncogenic alteration in the *PI3K–AKT–mTOR* pathway, which is a potential target for numerous inhibitors [6]. Furthermore, recent studies have demonstrated that the inhibitory effect mediated by PD-1 is predominantly achieved through the PI3K-Akt signaling pathway, with PD-1 blocking *PI3K* activation through recruiting *SHP-2* [7]. The results of genetic testing of six patients with ovarian-teratoma-associated squamous cell carcinoma revealed a high tumor mutational burden and elevated PD-L1 expression [5]. *XCL1* may facilitate the interactions of PD-1 and PD-L1 within the tumor microenvironment, resulting in CD8 + T-cell dysfunction [6]. Such patients may benefit from immune checkpoint inhibitor therapy based on these findings, a hypothesis that is supported by several clinical case reports [7–9].

According to a previous review, only 1–2% of cases are diagnosed preoperatively, but this is based on data from 40 years ago, and it is thought that recent PET and MRI will be able to detect suspected cases with greater accuracy. Patients typically present with symptoms such as abdominal pain, abdominal distension, or palpable masses; a minority seek medical attention because of complications such as tumor torsion or rupture [10]. MRI and computed tomography (CT) are invaluable for preoperatively evaluating the malignant transformation of teratomas [4, 11]. Key MRI features indicative of malignant transformation include a thickened cystic wall, the presence of solid components, and enlargement of the surrounding tissues or peritoneal involvement. The characteristic CT findings include fat-containing components and enhanced solid areas. Patient 1 presented with a solid cystic mass and multiple enlarged lymph nodes in the retroperitoneum and at the lipid-fluid interface on MRI, consistent with the diagnosis of malignant teratoma, as described in the literature. Elevated levels of the serum tumor markers SCC, CA125, CA19-9, and CEA are frequently observed in patients with squamous cell carcinomas arising from teratomas [12]. In this study, the CA19-9 and CA125 levels of both patients were elevated. However, the absence of squamous cell carcinoma

antigen measurements limited the interpretation of these findings. Malignant teratomas exhibit aggressive behavior and have poor prognoses and high mortality rates compared with epithelial tumors. The key prognostic factors include tumor stage, histologic grade, patient age, tumor size, presence of squamous cell carcinoma, CA125 levels, and extent of surgical resection [13, 14]. Li et al. reported that the five-year survival rates were 85.8%, 39.1%, 26.2%, and 0% for stages I, II, III, and IV disease among 435 patients, respectively [15].

Malignant teratoma transformation is typically treated following the protocols for epithelial or malignant germ cell tumors. Comprehensive surgical staging is recommended for early stage disease, whereas cytoreductive surgery is recommended for advanced stages [10]. The need for systematic lymphadenectomy remains a subject of considerable debate within the medical community [15, 16]. No standardized approach exists for postoperative adjuvant treatment, although adjuvant chemotherapy may improve the prognosis of patients with stage IB or higher disease [10]. Postoperative platinum-based combination chemotherapy is recommended for teratomas identified as squamous cell carcinomas given the efficacy of platinum-based chemotherapy in the treatment of various cancers, including gynecological squamous cell carcinomas [7]. The bleomycin + etoposide + cisplatin (BEP) regimen has also produced favorable outcomes [17]. However, the potential benefits of radiotherapy remain unclear and require further investigation [10].

Several critical issues emerged during this study that warrant an in-depth analysis. The first is the selection of the surgical approach. Both patients in this study demonstrated a strong preference for fertility preservation, rendering the feasibility of fertility-sparing surgical approaches a primary consideration in their treatment planning. The mortality rates do not substantially differ between fertility-preserving and radical surgery in patients with stage IA or IC disease, with successful pregnancies being reported [10, 15]. However, data on fertility-preserving surgery in patients with advanced-stage disease are limited. Peluso et al. reported a case of a young woman with stage IVB disease who underwent fertility-preserving surgery and was subsequently referred to a reproductive endocrinology department [18]. This study adhered to the NCCN guidelines on preserving the fertility of patients with germ cell tumors [15]. A fertility-preserving strategy was ultimately adopted for both patients following comprehensive evaluation and multidisciplinary discussions as well as considering the wishes of the patients and their families. Both patients postoperatively received GnRH-a therapy to protect ovarian function, and regular menstruation resumed in both patients after the discontinuation of the medication. Fertility preservation is crucial for women who have not yet given birth, although a consensus on the optimal treatment strategy for young patients has yet to be established. The second limitation relates to the selection of postoperative chemotherapy regimens: both patients were histologically diagnosed with squamous cell carcinoma. Platinum-based chemotherapy regimens were prioritized in this study on accordance with previous studies. However, recurrence and metastasis occurred during the course of chemotherapy in Patient 1, suggesting the occurrence of platinum resistance, although the precise mechanism of this resistance remains unclear. We hypothesized that this platinum resistance was associated with *TP53* gene mutations based on the genetic test results of the patient. Although *TP53* gene mutations in certain patients with ovarian cancer have been linked to platinum resistance and an increased risk of recurrence, not all *TP53* mutations result in platinum resistance [19]. Therefore, further studies are required to validate these preliminary observations. The third limitation relates to the timing of immunotherapy intervention: two patients at different stages of the disease received immunotherapy at distinct time points, with favorable therapeutic outcomes in both. Recurrence and metastasis developed during postoperative chemotherapy in Patient 1; however, a complete response was achieved following the administration of PD-1 inhibitors. Patient 2 was diagnosed in the early stage of the disease. The risk of recurrence and metastasis remains high given the rarity of squamous cell carcinoma arising from teratomas, the high degree of malignancy, and the age of the patient. Early intervention may more effectively activate the host immune system, thereby suppressing tumor progression and preventing metastasis, as demonstrated by the increased use of immunotherapy in early stage tumor treatment. This study demonstrates that immunotherapy has the potential to improve the prognosis of early stage squamous cell carcinoma arising from teratomas. This study provides valuable data to support future immunotherapy research. Fourth, the potential applications of PARP inhibitors are highlighted. The test results for Patient 2 showed *HRD* positivity, providing a theoretical foundation for the use of PARP inhibitors (PARPis) in the event of subsequent recurrence or metastasis. PARPis are expected to be viable therapeutic options if disease progression occurs.

In conclusion, teratomas with malignant transformation are characterized by high recurrence rates, high mortality rates, and poor response to chemotherapy, which underscore the urgent need to explore new treatment strategies to improve patient survival. The results of this study demonstrate that combination immunotherapy can considerably improve patient prognosis without increasing the incidence of side effects. Immunotherapy can be considered as a therapeutic strategy in clinical

decision making for advanced or recurrent cases, offering options for patients with this malignancy.

Abbreviations

MCTs	Mature cystic teratomas
MRI	Magnetic resonance imaging
Ca 19 – 9	Cancer antigen 19 – 9
Ca 12 – 5	Cancer antigen 12 – 5
NGS	Next generation sequencing
MSS	microsatellite stable
TMB	tumor mutation burden
NCCN	National Comprehensive Cancer Network
CEA	Carcino-embryonic antigen
HRD	homologous recombination deficiency
FIGO	International Federation of Gynecology and Obstetrics
SCC	Squamous-cell carcinoma antigen

Author contributions

J.L: Manuscript writing; Yx.G and Wx.W: Study design, manuscript revision, and final approval of the version to be published; Q.H: Manuscript revision; All listed authors have made substantial, direct, and intellectual contributions to the work and have approved the publication.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The Ethics Committee of Xinxiang Central Hospital approved this study. Patients signed informed consent for their data to be used for scientific purposes.

Consent for publication

Written informed consent was obtained from all participants, explicitly permitting the collection and use of clinical data for academic research.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

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