

Case report

Squamous cell carcinoma arising from a mature cystic teratoma of the ovary: Successful treatment with carboplatin, paclitaxel, and bevacizumab

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ABSTRACT

Ovarian mature cystic teratomas (MCT) are usually benign. However, squamous cell carcinoma (SCC) develops in 0.17–2% of MCT. Because of its low frequency, the optimal treatment for this disease is unclear. We present a case of SCC arising from MCT. Our patient was a 30-year-old nulliparous woman complaining of right lower abdominal pain, who was referred to our hospital for a pelvic solid mass with suspected malignant ovarian tumor. A diagnosis of SCC arising from MCT was suspected based on the elevation in SCC antigen and the imaging. After surgery to remove the tumor, the diagnosis was confirmed based on the pathology. Although the surgery by radical cytoreduction was optimal, the tumor showed early recurrence. Therefore, we administered combination chemotherapy, consisting of carboplatin, paclitaxel, and bevacizumab, followed by maintenance therapy with bevacizumab. Response to the chemotherapy regimen was complete and the patient was alive with no evidence of recurrence for 45 months after starting the initial surgery. We discuss the clinical characteristics of the malignant transformation of MCT and the treatment of SCC arising from MCT.

1. Introduction

Mature cystic teratomas (MCT) of the ovary, also known as dermoid cysts, are the most common ovarian germ cell tumor. MCT, which occurs during a woman's reproductive age, comprises 30–45% of ovarian tumors (Ulbright, 2005). Histologically, MCT encompasses three germ layers (ectoderm, mesoderm, and endoderm). MCT undergoes malignant transformation in 0.17–2% of cases (Hackethal et al., 2008). Although malignant transformation can evolve from any of the three germ layers, malignant transformation into squamous cell carcinoma (SCC), which arises from the ectoderm, accounts for 80% of the cases (Hackethal et al., 2008). Moreover, malignant transformation has a poor prognosis, with no standard treatment because it is so rare (Hackethal et al., 2008). In this report, we describe a patient with SCC arising from MCT. The patient responded completely to a chemotherapy regimen of carboplatin, paclitaxel, and bevacizumab.

2. Case report

A 30-year-old nulliparous woman with a two-month history of right lower abdominal pain was referred to our hospital for a pelvic solid mass with suspected malignant ovarian tumor. Her medical and family

history was insignificant. On admission, examination demonstrated a movable mass as large as a newborn's head in the right lower quadrant. Pelvic ultrasonography showed a 9 × 9 cm right ovarian tumor that was suspected of invading the uterus. The pap-smear was negative for malignant cells. The serum levels of tumor markers were as follows: SCC, 15.1 ng/mL (normal range < 1.5); CA125, 35.9 U/mL (normal range < 35.0); and CA19-9, 386.2 U/mL (normal range < 35.0). Magnetic resonance imaging showed a pelvic multilocular cystic mass with a diameter of 9.8 × 6.2 cm and high and low signal intensities on the T1-weighted images. The lesion had high signal intensity on the T1-weighted images (Fig. 1A), which was as low as that of fat on the fat-suppressed contrast-enhanced T1-weighted image (Fig. 1B). The lesion had low intensity on the T1-weighted images, which was enhanced and had high signal intensity on the fat-suppressed contrast-enhanced T1-weighted image. These results suggested that the ovarian tumor was composed of multilocular cysts, fatty components, and a solid part. A positron emission tomography (PET) showed fluorodeoxyglucose (FDG) accumulation in the solid part of the tumor (Fig. 1C), indicating metastasis to the right external iliac lymph node (Fig. 1D) and a Douglas fossa disseminated lesion (Fig. 1E). Because the patient hoped to preserve fertility and refused a complete reduction at the initial surgery, we performed a right salpingo-oophorectomy, and biopsied the right

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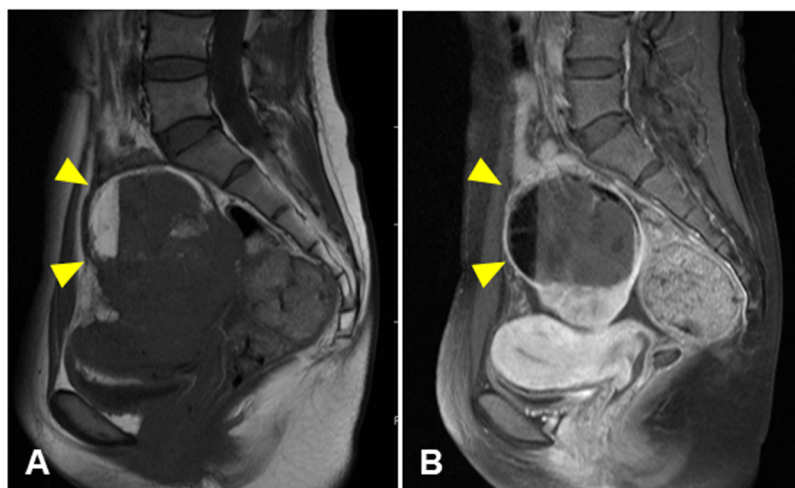
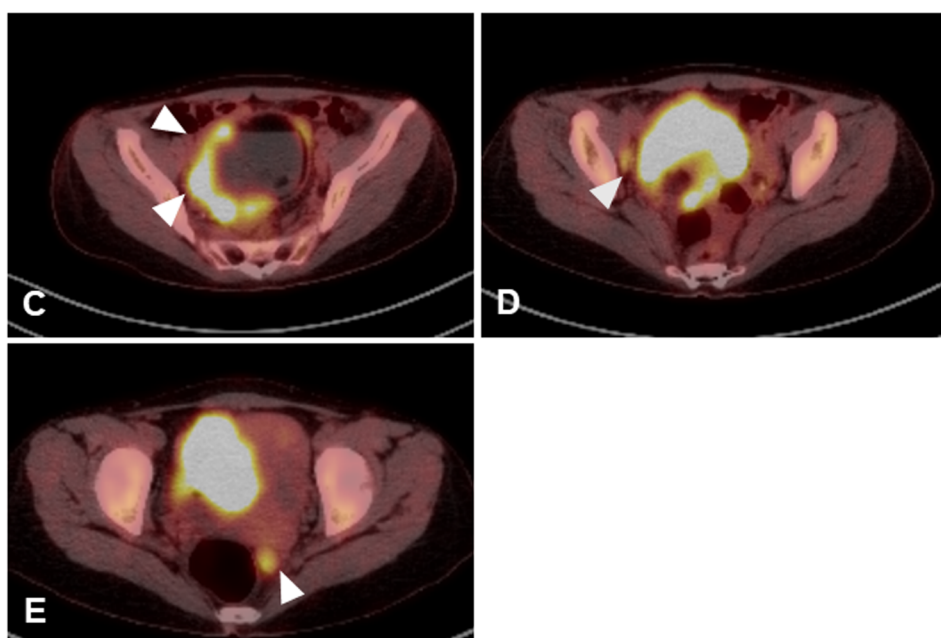


Fig. 1. Sagittal T1-weighted (A) and sagittal fat-suppressed contrast-enhanced T1-weighted (B) magnetic resonance images. A large 9.8×6.2 cm mass was observed behind the uterus. The lesion had high signal intensity on the T1-weighted images, which was as low as that of fat on the fat-suppressed contrast-enhanced T1-weighted image (yellow arrowhead). The intensity of the solid part was enhanced on the fat-suppressed contrast-enhanced T1-weighted image compared to that on the T1-weighted image. FDG-PET showed high FDG accumulation in the solid part of the right ovary tumor (white arrowhead) (C), the right external iliac lymph node (D), and a Douglas fossa disseminated lesion (E).



obturator lymph node. Intraoperatively, we discovered that the right ovarian tumor had adhered to the posterior surface of the uterus and spread into the broad ligament. Dissemination was observed on the rectal surface and sacral uterine ligament. Swelling of the para-aortic lymph nodes was identified by palpation. The disease stage appeared to be higher than stage IIB. Macroscopic appearance of the 12×8 cm right ovarian tumor revealed multilocular cysts containing fat, sebum, and hair (Fig. 2A). In pathological examination, an area with malignant transformation into SCC was identified with a nest of malignant squamous cells infiltrating the stroma with keratinized pearls (Fig. 2B). These findings indicated SCC arising from MCT. The cytologic examination of ascites was negative. We proposed radical surgery to debulk the tumor as much as possible and obtained patient consent. Subsequently, we performed total abdominal hysterectomy (TAH), left salpingo-oophorectomy (SO), omentectomy (OME), pelvic lymphadenectomy (PLD), para-aortic lymphadenectomy (PAN), proctectomy, and colostomy. We observed tumor dissemination on the surface of the

rectum and the peritoneum of the pelvic cavity, but not in the upper abdomen. The patient was diagnosed with a stage IIIA1(i) SCC arising from MCT based on the International Federation of Gynecology and Obstetrics (FIGO2014). Three weeks after the surgery to debulk the tumor, computed tomography (CT) showed swelling of the right obturator lymph node, and ascites in the pelvic cavity, peritoneal dissemination (Fig. 3A and B). Tri-weekly paclitaxel (135 mg/m^2), carboplatin (AUC 5), and bevacizumab (15 mg/kg) were administered for six courses as adjuvant chemotherapy. Bevacizumab was not administered in the first and second courses due to proteinuria. After completion of chemotherapy (paclitaxel, carboplatin, and bevacizumab), swelling of the right obturator lymph node decreased, and neither ascites nor peritoneal dissemination showed on the CT scan (Fig. 3C and D). No FDG accumulation was observed in these lesions. Tri-weekly bevacizumab (15 mg/kg) was administered for 18 courses as maintenance therapy. The patient was alive with no evidence of recurrence for 45 months after the initial surgery.

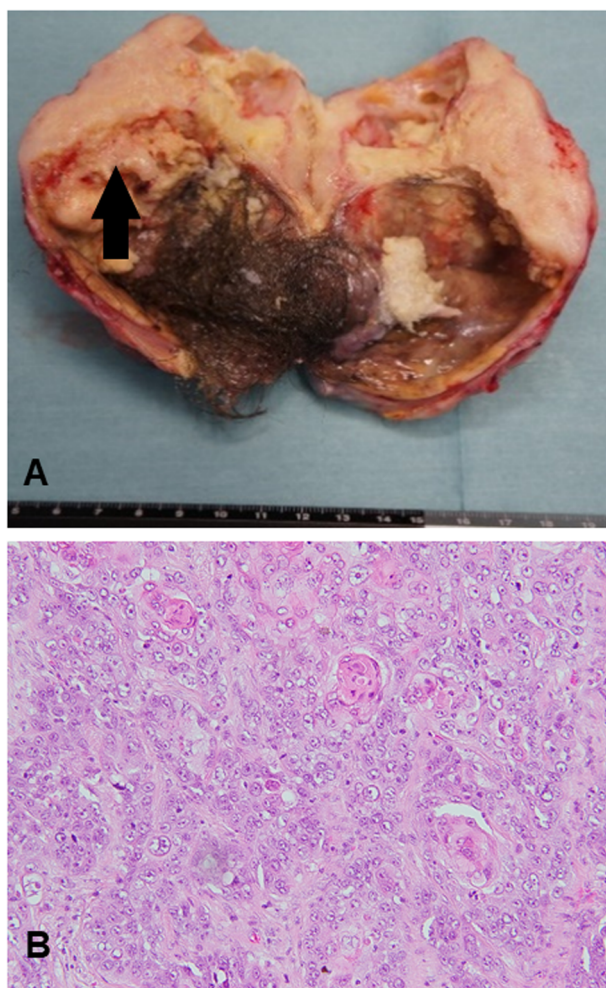


Fig. 2. Macroscopic appearance of the right ovarian tumor showed fat, hair, and solid components (arrow) (A). Squamous cell carcinoma is shown within the mature cystic teratoma (H&E, $\times 40$) (B). Nest of malignant squamous cells infiltrating the stroma with keratinized pearls (H&E, $\times 200$) (C).

3. Discussion

To the best of our knowledge, this is the first case report demonstrating that combination chemotherapy with carboplatin, paclitaxel, and bevacizumab was effective in treating patients with SCC arising from MCT.

Ovarian MCTs are usually benign; however, malignancy arises in 0.17–2% of the teratomas (Hackethal et al., 2008). The optimal adjuvant therapy for SCC arising from MCT has not yet been systemically assessed because it is such a rare disease. Chen et al. reported that postoperative adjuvant chemotherapy improved survival rate for patients with advanced SCC arising from MCT, but postoperative radiotherapy did not positively affect oncologic outcomes in these patients (Chen et al., 2008). Hackethal et al. also showed that complete resection, including hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy, followed by adjuvant chemotherapy combined with an alkylating drug was associated with a higher survival rate compared to postoperative radiotherapy in patients with advanced disease

(Hackethal et al., 2008). Yoshida et al. summarized 21 patients who received radiotherapy for SCC arising from MCT (Yoshida et al., 2016). In this study, seven patients were stage III, and 14 were stage II. All patients underwent surgery combined with postoperative adjuvant therapies. Thirteen were treated with radiation plus chemotherapy and 8 patients received radiation only. The 2- and 3-year survival rates were 43.3% and 34.7%, respectively. SCC is a common histologic subtype in the uterine cervix which is thought to be radiosensitive. Therefore, SCC arising from MCT may respond well to radiotherapy. However, radiotherapy or chemoradiotherapy might be less effective in patients with advanced-stage disease.

Previous study demonstrated that combination chemotherapy with carboplatin and paclitaxel is effective in treating SCC arising from MCT, resulting in improved survival in most patients with advanced-stage disease (Sakuma et al., 2010). Phase III clinical studies demonstrated that combining bevacizumab with carboplatin and paclitaxel improved survival in advanced and recurrent ovarian cancer patients (Burger et al., 2011; Aghajanian et al., 2012) and showed favorable oncologic outcomes in advanced cervical cancer patients (Tewari et al., 2014). In our case, the tumor showed early recurrence after surgery, suggesting that the tumor was aggressive. Therefore, we used the combination chemotherapy consisting of carboplatin, paclitaxel, and bevacizumab. This regimen resulted in a complete response despite early recurrence after surgery, suggesting that bevacizumab might enhance the efficacy of combination chemotherapy with carboplatin and paclitaxel in SCC arising from MCT.

Recent studies demonstrated that XCL1 is specifically overexpressed in SCC arising from MCT compared with benign MCT (Tamura et al., 2020). XCL1 expression in tumor cells is associated with the number of tumor-infiltrating CD8-positive killer T cells and PD-L1 expression in tumor cells. The inflammatory cytokine IL6 is predictive of therapeutic benefit from bevacizumab when combined with carboplatin and paclitaxel in ovarian cancer (Alvarez Secord et al., 2020). Collectively, these studies suggest that the enhancement in efficacy with the addition of bevacizumab to carboplatin and paclitaxel for the treatment of SCC arising from MCT may be related to the immune system.

A study analyzing gene expression of SCC arising from MCT demonstrated a high frequency of *TP53* and *PIK3CA* mutation in this disease (Tamura et al., 2020). *TP53* and *PIK3CA* mutations might have a crucial role in the malignant transformation from MCT. In that study, most SCC arising from MCT harbored at least one known oncogenic alteration in the PI3K-AKT-mTOR pathway that was targeted by many inhibitors (Tamura et al., 2020). Although the tumor showed a complete response to adjuvant chemotherapy, including carboplatin, paclitaxel, and bevacizumab, in our case, profiling gene expression of SCC arising from MCT might indicate an appropriate adjuvant therapy in each individual case.

In conclusion, we described our experience successfully treating a patient with SCC arising from MCT with adjuvant chemotherapy, including carboplatin, paclitaxel, and bevacizumab. Bevacizumab might have been one of the treatment options for improving oncological outcomes in patients with advanced-stage disease.

Author contribution

MF, TO and SN designed the study. MF and TO wrote the main manuscript and prepared all figures. All authors treated the patients. All authors reviewed and approved the final manuscript.

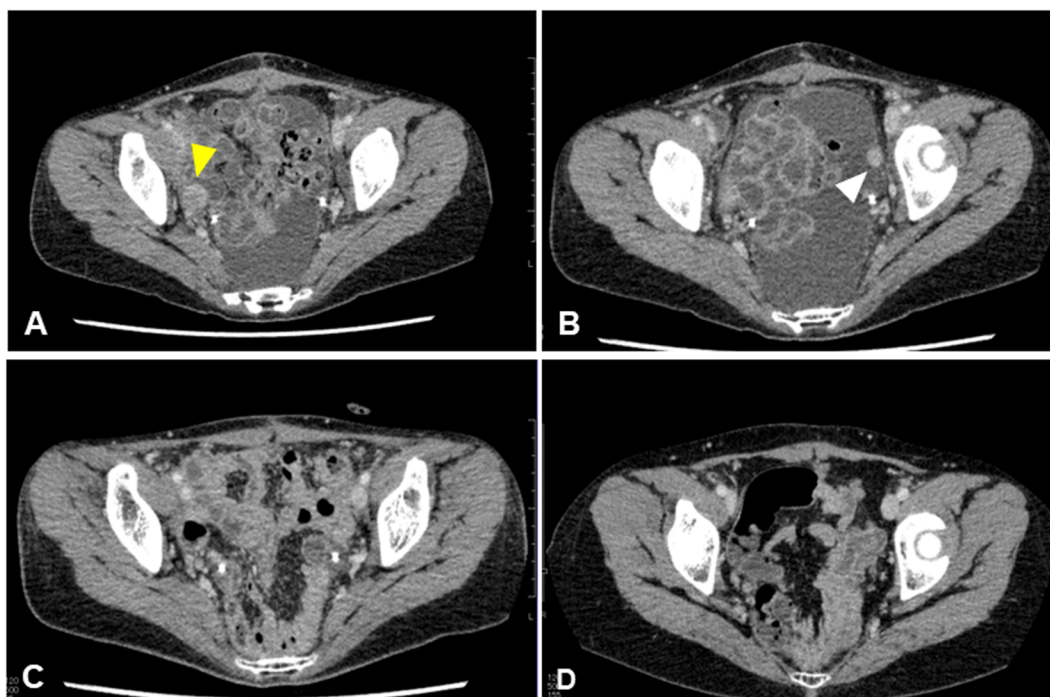


Fig. 3. At three weeks after the surgery to optimally debulk the tumor, computed tomography (CT) showed swelling of the right obturator lymph node (yellow arrowhead) (A), and ascites in the pelvic cavity, peritoneal dissemination (white arrowhead) (B). After completion of chemotherapy (paclitaxel, carboplatin, and bevacizumab), swelling of right obturator lymph node was decreased (C), and CT showed neither ascites nor peritoneal dissemination (D).

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: 'S. Nagase received lecture fees from Chugai Pharmaceutical CO., LTD. Other authors have no conflict of interest.'

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