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Case report

Refractory ovarian squamous cell carcinoma arising from a seromucinous borderline tumor with squamous overgrowth: A case report

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ABSTRACT

Ovarian squamous cell carcinoma (SCC) is rare, and most cases arise from ovarian teratomas. Herein, we present a case of ovarian SCC arising from an ovarian seromucinous borderline tumor (SMBT) with squamous overgrowth. A 71-year-old woman an underwent emergency laparotomy due to the rupture of a right ovarian tumor suspected to be a borderline or malignant tumor. We performed a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and partial omentectomy. The postoperative diagnosis was stage IC3 ovarian SCC arising from the SMBT with a squamous overgrowth. Subsequently, she underwent six cycles of combination therapy comprising paclitaxel and carboplatin. Two months after the last chemotherapy treatment, she presented with back pain. A CT scan showed a 14 mm pelvic tumor affecting the ureter, leading to right hydronephrosis. The patient underwent tumor resection and ureteroureterostomy. The pathological diagnosis was keratinizing SCC, representing ovarian cancer recurrence. Eight months after the removal of the recurrent tumor, we found a 35 mm recurrent pelvic tumor causing right hydronephrosis. Additionally, a 20 mm pleural dissemination was identified. Comprehensive genome profiling of recurrent tumor revealed genomic abnormalities in *TP53*, *ARID1A*, *PTEN*, *PIK3R1*, and *CDKN2A/2B*. Regarding immunotherapy biomarkers, the microsatellite instability test result was negative, the tumor mutation burden was low, and PD-L1 was highly expressed. The patient was referred to another hospital for participation in an immunotherapy clinical trial for ovarian SCC. This case indicates that refractory ovarian SCC can arise from SMBT. Further evaluation of additional cases is required to identify the molecular biological characteristics of ovarian SCC.

1. Introduction

Ovarian squamous cell carcinoma (SCC) is rare. Most cases arise from ovarian teratomas, and cases classified as stage II or higher have a poor prognosis (Hackethal et al., 2008). In addition to ovarian teratomas, ovarian SCC can originate from ovarian endometriosis, Brenner's tumors, or metastasis from SCCs in other organs. A pure ovarian SCC of unknown origin has also been reported (Park and Bae, 2015). Although ovarian SCC has a poorer prognosis than serous ovarian carcinoma based on the Surveillance, Epidemiology, and End Results (SEER) database (Zhang and Ma, 2020), the differences in the clinicopathological and molecular biological characteristics based on each origin site have not yet been fully elucidated.

There have been several reports of ovarian SCC associated with borderline ovarian tumors (D'Angelo et al., 2010, Bak et al., 2023). An ovarian seromucinous borderline tumor (SMBT) contains a combination of serous and endocervical-type mucinous epithelia as well as endometrioid, indifferent, and squamous-type epithelium (Kurman et al., 2016}. Nagai et al. identified four cases of a rare subtype of SMBT, previously known as a mixed-epithelial papillary cystadenoma of borderline malignancy of the Müllerian type, with squamous overgrowth. D'Angelo et al. reported an SCC arising from an SMBT with marked squamous differentiation (D'Angelo et al., 2010). Herein, we present a highly unusual case of stage IC3 ovarian SCC arising from an SMBT with squamous overgrowth. The tumor was refractory to treatment and relapsed in the pelvis 2 months after the patient received adjuvant platinum-based chemotherapy following complete tumor resection.

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2. Case presentation

A 71-year-old multiparous woman with no significant medical history visited her local physician with symptoms of lower abdominal pain. A 13 cm right ovarian tumor was identified, and the patient was referred to our hospital for further examination and treatment. Magnetic resonance imaging revealed a right ovarian tumor with enhanced small nodules and a reduction in the apparent diffusion coefficient values, raising the suspicion of a borderline or malignant tumor (Fig. 1A and 1B). Computed tomography (CT) showed no evidence of metastases. Tumor marker tests revealed elevated levels of squamous cell carcinoma antigen (SCC-Ag) at 11.6 ng/ml, and carcinoembryonic antigen (CEA) at 12.1 ng/ml. Carbohydrate antigen 125 (CA125) and carbohydrate antigen 19–9 (CA19-9) levels were within normal ranges, at 26.3 U/ml and 24.9 U/ml, respectively. Four days after the initial visit, she presented with worsening abdominal pain. Blood tests revealed elevated levels of inflammatory markers (white blood cell count: 12,500/μl, C-reactive protein: 20.05 mg/l), and CT imaging showed a slight increase in ascitic fluid and a mild increase in fat tissue density in the abdominal cavity. The patient was diagnosed with peritonitis due to ovarian tumor rupture and underwent emergency exploratory laparotomy. The right ovarian tumor ruptured, consistent with the preoperative diagnosis and firmly adhered to the uterus and retroperitoneum. No other apparent tumors were observed in the abdominal cavity. Small amounts of brown mucoid fluid are observed in the peritoneal cavity. Ensuing ascitic fluid cytology revealed atypical cells; however, it was challenging to determine their malignancy. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, and partial omentectomy were performed, and the tumor was completely resected.

The postoperative diagnosis was a stage IC3 ovarian SCC (pT1cNXM0). The ovarian tumor showed wall thickening, but no prominent solid part (Fig. 1C). The tumor was mainly comprised of papillary squamous components with no or mild atypia (Fig. 1D). A few small areas measuring 10 × 6 mm exhibited severe cellular atypia and stromal invasion with keratinization, which were diagnosed as invasive SCC (Fig. 1E). Seromucinous epithelial cells with borderline malignancy were observed in parts of the tumor and were continuous with squamous epithelial cells (Fig. 1F). Immunostaining was positive for ER, PAX8, and CA125, indicating that the seromucinous epithelial cells originated from the Müllerian duct (Supplementary Fig. 1). We evaluated differences in the protein expression of several key genes in both SCC and seromucinous borderline tumors. p53 overexpression was observed in SCC but not in seromucinous borderline tumors (Supplementary Fig. 2). p16 immunostaining demonstrated cytoplasmic staining of SCC without nuclear staining. Notably, this staining pattern did not indicate diffuse positivity, raising the possibility of Human papillomavirus infection (Supplementary Figure 3). Ovarian endometriosis was not identified; however, the pathological identification of uterine adenomyosis and peritoneal endometriosis suggested the presence of endometriosis (Supplementary Figure 4). There were no findings indicative of a teratoma or Brenner tumor, and no atypia or cancer in the uterus. There were no findings of endometriosis-related ovarian cancer, such as clear cell carcinoma or endometrioid carcinoma. Finally, she was diagnosed with SMBT with squamous overgrowth in the background of endometriosis, which developed into ovarian SCC.

Six weeks after surgery, the patient received six doses of intravenous carboplatin and paclitaxel (175 mg/m^2). CT imaging after six courses showed no residual tumor, and blood SCC-Ag levels decreased from 13.4 ng/ml preoperatively to 1.0 ng/ml at the end of one period of chemotherapy. Two months after the adjuvant chemotherapy, the patient presented with back pain. CT imaging showed a 14 mm pelvic tumor affecting the ureter, leading to right hydronephrosis (Fig. 2A and B). Despite the platinum-resistant recurrence in the patient, determining whether it was SCC recurrence or ruling out ureteral carcinoma was challenging. Therefore, tumor excision and ureteroureteral anastomosis were performed. The pathological diagnosis was keratinizing SCC, indicating ovarian cancer recurrence (Fig. 2C and D). After consultation, the decision was made to follow up with the patient without postoperative chemotherapy.

Eight months after the removal of the recurrent tumor, we found a

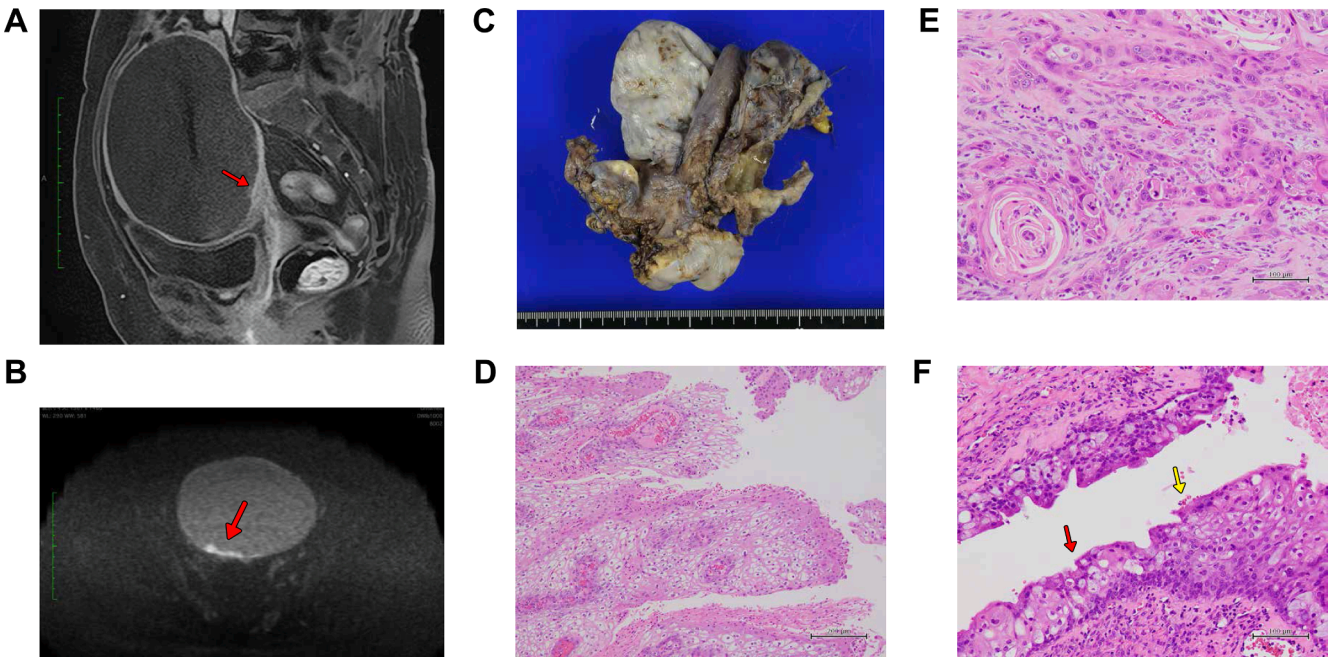

Fig. 1. Magnetic resonance imaging (MRI) and pathological findings for primary right ovarian tumor. A Sagittal contrast-enhanced T1-weighted MRI. A right ovarian tumor with enhanced small nodules (red arrow) is detected. **B** Axial diffusion-weighted MRI imaging. A right ovarian tumor with a reduction in the apparent diffusion coefficient (red arrow) is detected. **C** Macroscopic findings of the primary tumor. **D** Representative images of H&E-stained squamous overgrowths (200 × magnification). **E** Representative images of H&E staining of invasive squamous cell carcinoma (SCC) with keratinization (200 × magnification). **F** Representative images of H&E staining of the seromucinous epithelium (red arrow) transitioning to the squamous epithelium (yellow arrow) (200 × magnification). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

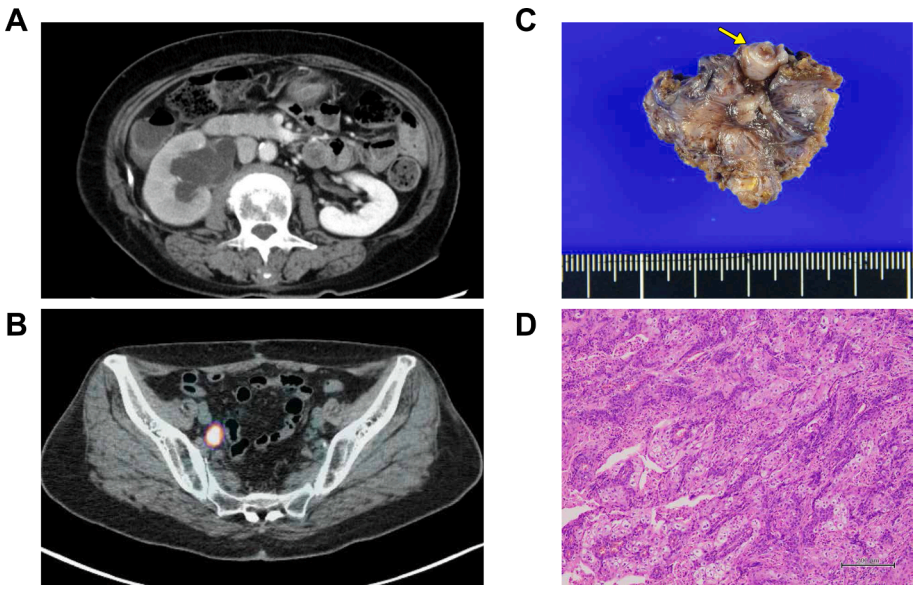

Fig. 2. Computed tomography (CT) image and pathological findings for recurrent tumor. **A** Axial CT image of the right hydronephrosis. **B** Axial FDG-PET CT image of the recurrent tumor. **C** Macroscopic findings of the primary tumor. Yellow arrow indicates the ureter. **D** Representative images of hematoxylin and eosin staining of the recurrent tumor (200 × magnification). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

35 mm recurrent pelvic tumor causing right hydronephrosis. Additionally, a 20 mm pleural dissemination was identified. The SCC-Ag levels increased again, at 17.4 ng/ml. A comprehensive genome profiling test (FoundationOne®CDx) using recurrent ovarian SCC identified pathogenic genetic alterations in *TP53*, *ARID1A*, *PTEN*, *PIK3R1*, and *CDKN2A*. The microsatellite instability test result was negative, and the tumor mutation burden (TMB) was low. We found that PD-L1 (clone 28–8) was highly expressed (tumor proportion score, 60 %; Table 1 and Supplementary Figure 5). Although the genome profiling test did not lead to the recommendation of molecular-targeted therapy, the patient was eligible for a phase II trial of pembrolizumab for ovarian SCC (NCT05737199) and was referred to another hospital.

3. Discussion

We present a highly unusual case of ovarian SCC arising from an SMBT with squamous overgrowth, detailing its treatment course and genomic abnormalities. Seromucinous carcinoma, which was removed as a subtype of endometrioid carcinoma in the WHO2020 classification, is predominantly composed of serous and endocervical-type mucinous epithelium with foci containing clear cells and areas of endometrioid and squamous differentiation (Siegel et al., 2020). In contrast, the present case was predominantly composed of squamous epithelium with minimal endocervical-type mucinous epithelium, which is not consistent with seromucinous carcinoma. Furthermore, the area histologically diagnosed as an invasive carcinoma exhibited typical SCC with keratinization. Therefore, we considered it appropriate to diagnose this case as ovarian SCC even though the tumor originated from a rare subtype of SMBT.

Table 1
Summary of cancer genetic testing results.

Genetic abnormalities	*TP53* R273H *PTEN* R233*, Y225* *CDKN2A* V59fs*58 *CDKN2B* G74fs*84 *ARID1A* Q439* *PIK3R1* S460_R461 > G
Homologous Recombination status	HRD not detected
Tumor Mutation Burden (TMB)	Low (7 Muts/Mb)
Microsatellite Instability (MSI)	Stable
PD-L1 immunohistochemistry	Positive (TPS 60 %)

HRD: homologous recombination deficiency, TPS: tumor proportion score.

SMBT is thought to be derived from or associated with endometriosis in 30–50 %, sharing common genetic abnormalities with endometrioid and clear-cell tumors (Yun et al., 2022, Sasamori et al., 2022). SMBT with squamous overgrowth represents a rare subtype of SMBT, with a median age of 56.5 years, which is older than that of patients with typical SMBT, with a median age of 39.7 years. All patients with this subtype were found to have endometriosis with no reported recurrence, and the SCC-Ag level was elevated in one evaluated case (Nagai et al., 2003). In the present case, the patient was older than the previously reported age range for SMBTs or SMBTs with squamous overgrowth. Although the prognostic differences based on the origin of ovarian SCC have not been extensively evaluated, ovarian SCC associated with endometriosis has an extremely poor prognosis. Most cases are diagnosed at an advanced stage, with up to 80 % of patients dying within 6 months of diagnosis (Xu and Li, 2018). Although adjuvant chemotherapy with paclitaxel, carboplatin, or cisplatin has been reported to improve survival in some cases (Xu and Li, 2018), the tumor in our patient displayed a resistance to platinum-based chemotherapy. This case suggests that refractory SCC may arise from SMBT. Patients with SMBTs, particularly in older adults, those with elevated SCC-Ag levels, and those with squamous hyperplasia, should be carefully evaluated for the presence of SCC.

Although two reports of ovarian SCC appear to have occurred under similar conditions (D'Angelo et al., 2010, Bak et al., 2023), this is the first report of a comprehensive genomic profiling of ovarian SCC associated with SMBT. Comprehensive analyses have revealed a notably high frequency of pathogenic mutations in the tumor suppressor protein P53 (*TP53)* in SCCs arising from ovarian teratomas (Tamura et al., 2020). In this case, we identified a *TP53* pathogenic mutation (R273H). Immunostaining showed overexpression of TP53 in SCC and no detectable expression in seromucinous borderline tumors. This suggests that *TP53* mutations play a significant role in the development of SCC. In addition, we also identified *ARID1A* and *PIK3R1* pathogenic mutations (Q439* and S460_R461 > G) that have not been previously reported in SCC derived from ovarian teratomas (Tamura et al., 2020). These mutations are common in endometrial and endometriosis-associated

ovarian cancers (Cancer Genome Atlas Research Network et al., 2013, Driva et al., 2023). In addition, an *ARID1A* mutation may be linked to the molecular biology of SMBTs (Wu et al., 2012). Furthermore, these mutations have been identified in endometriotic and normal endometrium (Suda et al., 2018). These findings are consistent with the presumption that SCC may develop in association with endometriosis or SMBT in our case. We were unable to compare the genetic mutation profiles of SMBT and SCC primary tumors in this study. Accumulating more cases and conducting detailed studies are necessary to characterize the molecular biology of ovarian SCC.

More than half of SCC cases arising from ovarian teratomas exhibit programmed death receptor-1 (PD-1) expression and high tumor-infiltrating CD8-positive lymphocyte counts, suggesting the effectiveness of immune checkpoint inhibitors (Tamura et al., 2020). A phase II trial of pembrolizumab for the treatment of ovarian SCC (NCT05737199) is currently ongoing in Japan. Although the biological mechanism underlying high PD-L1 expression in this case is unknown, anti-PD-1 antibodies may be effective, as demonstrated in SCC arising from ovarian teratomas. Our case highlights the potential differences in genetic abnormalities among ovarian SCCs, based on their site of origin. In conclusion, refractory SCC can arise from ovarian SMBT and this possibility should be considered. The profile of genetic abnormalities in ovarian SCC may also differ based on the site of origin. Further evaluation of additional cases is required to identify the molecular biological characteristics of ovarian SCC.

Declarations

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report. A copy of the written consent form is available for review by the editor-in-chief of this journal upon request.

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CRediT authorship contribution statement

Ryo Tamura: . **Naohisa Kushiya:** Writing – review & editing. **Masayuki Yamaguchi:** Writing – review & editing. **Nobumichi Nishikawa:** Writing – review & editing. **Teiichi Motoyama:** Writing – review & editing. **Takashi Kawasaki:** Writing – review & editing. **Akira Kikuchi:** Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2024.101323.

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