

CASE REPORT

Pure primary ovarian squamous cell carcinoma with homologous recombination deficiency: a case report

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Abstract

Pure primary ovarian squamous cell carcinoma (SCC) is a rare histological type with a poor prognosis. Herein, we present the first reported case of advanced pure primary ovarian SCC with homologous recombination deficiency (HRD). A 65-year-old woman who underwent emergency surgery because of acute abdominal pain was diagnosed with SCC of the ovary and was referred to our department for further treatment. Thorough investigations revealed no signs of other primary sites of SCC except for the left ovary. Postoperative positron emission tomography-computed tomography showed residual tumor. Since pure primary ovarian SCC typically shows a poor response to chemotherapy, we decided to perform debulking surgery. Total abdominal hysterectomy, right salpingo-oophorectomy, pelvic lymphadenectomy, para-aortic lymphadenectomy, bowel resection and left partial ureterectomy were performed. Postoperatively, there was no residual tumor larger than 1 cm. Postoperatively, she developed pelvic infection that prolonged her hospital stay due to the need for antibiotics. However, there were no other perioperative complications and she was discharged. SCC with keratinization was observed on histopathological examination of metastatic lymph nodes. An HRD companion diagnostic test performed on the resected specimen was positive for HRD (score 57) and negative for *BRCA* 1/2 mutations. She received six courses of paclitaxel and carboplatin followed by maintenance therapy with niraparib, which is continuing. There are no signs of recurrence as of the one-year follow-up after surgery. We presented a rare case of advanced pure primary ovarian SCC with HRD. Complete surgical removal of HRD-positive pure primary ovarian SCC may lead to long-term survival with subsequent chemotherapy followed by maintenance therapy with poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors.

Keywords

Primary ovarian squamous cell carcinoma; Homologous recombination deficiency; Debulking surgery; Chemotherapy; Poly (adenosine diphosphate-ribose) polymerase inhibitor

1. Introduction

Pure primary ovarian squamous cell carcinoma (SCC) is an ovarian cancer in which the malignant tissue consists entirely of SCC without a background of mature cystic teratoma or other malignancies. The first documented case of pure primary ovarian SCC was reported in 1964 by Black and Benitez [1]. In 2019, Koufopoulos *et al.* [2] reviewed 36 cases reported from 1964 to 2018. Since then, only a few case reports have described this rare clinical entity. Owing to the rarity of pure primary ovarian SCC, no standard treatment protocol has been established for this tumor. The prognosis of advanced-stage cases is poorer than that of generalized epithelial ovarian cancer and previous reports have identified the need to develop new treatment methods. We report a previously unreported case of pure primary ovarian SCC with

homologous recombination deficiency (HRD).

2. Case report

The patient was a woman in her mid-60s. Her obstetric history was Gravida 3 Para 3, with all three pregnancies culminating in normal vaginal deliveries. The past medical and family history were unremarkable. She had no history of smoking. She visited the emergency room of a local hospital because of left-sided lower abdominal pain for 1 month. Computed tomography showed an enlarged left ovary (Fig. 1a). Emergency surgery was performed on the same day due to suspected ovarian torsion. Intraoperative examination revealed a left ovarian tumor, which had partially invaded the left ureter and sigmoid colon and was firmly adherent to the pelvic wall. She underwent left salpingo-oophorectomy, sigmoid

colon resection and colostomy, but the residual tumor persisted in the pelvic wall. Since the ovarian tumor was adherent to the sigmoid colon, the left adnexa and sigmoid colon were removed en bloc. A stoma was created for the sigmoid colon, and the operation was terminated.

On gross examination of the surgical specimen, the left ovary was firmly adhered to the sigmoid colon with suspected invasion of the latter by ovarian cancer. Histopathological examination revealed atypical cells with a high nucleocytoplasmic ratio with keratinization forming a full follicle that had infiltrated into the ovarian stroma and fallopian tube stroma. These findings were indicative of SCC (Fig. 2). Immunohistochemical analysis showed strong and diffuse positivity for Creatine Kinase (CK)5/6, p40 and p16, while a partial mottled staining pattern was observed for CK7 and Estrogen Receptor (ER). There were no findings of pre-existing lesions such as teratoma, dermoid cyst or endometrioma. Postoperative positron emission tomography-computed tomography (PET-CT) showed enlarged para-aortic lymph nodes (Fig. 1b), and the patient was referred to our department for further treatment. Detailed investigations revealed no other primary sites of SCC. Her cervical and urine cytology were negative, and no skin or lung lesions were detected on visual or imaging examinations. In the absence of any evidence of SCC in other organs as the primary malignancy, we diagnosed this case as pure primary ovarian SCC. Her serum SCC antigen and carcinoembryonic antigen levels were high (8.2 ng/mL and 53.0 ng/mL, respectively). Magnetic resonance imaging showed diffusion-limited nodules in the pelvis, which were suggestive of residual tumor and disseminated lesions. Additionally, the para-aortic lymph nodes below the renal vein, common iliac lymph node, and external iliac lymph node were enlarged. These areas coincided with the area of fluorodeoxyglucose accumulation in the postoperative PET-CT performed at the previous hospital. These imaging results indicated the feasibility of complete resection of the tumor, and given the low sensitivity of SCC to chemotherapy, we decided to perform debulking surgery. A left ureteral stent was placed preoperatively. Total abdominal hysterectomy, right salpingo-oophorectomy, pelvic lymphadenectomy, para-aortic lymphadenectomy, bowel resection and left partial ureterectomy were performed. The operation time was 10 hours and 11 minutes, and the blood loss was 1350 mL. The uterus and right adnexa were normal, and the disseminated lesions were located ventral to the rectum and involved the terminal ileum, cecum and jejunum. A seeding lesion was also present in the rectovaginal septum. The jejunal segment with the disseminated lesion was partially resected and anastomosed. The ileal segment involved in the disseminated lesion was resected, and the ileum was anastomosed with the ascending colon. The rectum was excised with the seeding lesion attached to the rectal side of the rectovaginal septum. Because a disseminated lesion had invaded the left ureter, the left ureter was resected in conjunction with the disseminated lesion, and a ureter-ureter anastomosis was performed. All enlarged lymph nodes were removed. Although there were scattered lesions in the jejunum and ileum, there was no residual tumor larger than 1 cm. Postoperatively, the patient developed pelvic infection which was treated conservatively with antibiotics. She was

discharged on postoperative day 22. Histologically, SCC with keratinization was seen in disseminated and metastatic lymph nodes and the surface of the uterine cervix, which had also invaded the cervical myometrium. However, there was no atypia in the squamous epithelium of the cervix, the epithelium was p16⁻, and no increase in Ki-67⁺ cells was observed, which ruled out cervical cancer as the primary lesion. To investigate whether this SCC was caused by human papillomavirus (HPV) infection, HPV testing (types 16, 18, 31, 33, 35, 52 and 58) was performed using polymerase chain reaction (PCR) on a paraffin block of the initial surgical specimen, but the results were negative (Fig. 3). Based on these results, a diagnosis of primary SCC of the left adnexa unrelated to HPV infection was established. The International Federation of Obstetrics and Gynecology (FIGO 2023) stage was IIIC2. The mychoice CDx (Myriad Genetic Laboratories, Inc, Salt Lake City, USA) test and the microsatellite instability (MSI) test were performed on the resected specimen. The Genomic Instability Score of 57 indicated a positive result but the test for *BRCA* 1/2 mutations was negative. The MSI test was negative. Five weeks after surgery, she received intravenous adjuvant chemotherapy with paclitaxel (175 mg/m²) and carboplatin (AUC6). Bevacizumab was not used in combination because of multiple gastrointestinal resections and partial ureteral resection. CT imaging after six courses showed no signs of recurrence or relapse; thereafter, niraparib (200 mg/day) as maintenance therapy was initiated. She did not experience any >Grade 2/3 adverse effects. As of 16 months after her surgery, there are no signs of recurrence and she is continuing to take niraparib orally.

3. Discussion

Ovarian SCC is a rare histologic subtype. In the majority of cases, ovarian SCC occurs due to malignant transformation of dermoid cysts [3, 4], endometriosis [5], or due to metastasis from other organs. True pure primary ovarian SCC with no evidence of originating from a benign ovarian tumor, as in the present case, is extremely rare. Some reports have implicated HPV infection as a causal factor for inducing the malignant transformation of mature cystic teratoma to SCC [2, 6]. However, our patient had negative cervical cytology and there was no evidence of cervical cancer or intraepithelial lesions in the excised uterine cervix. Moreover, HPV infection was ruled out by PCR.

In a previous study based on the Surveillance, Epidemiology, and End Results (SEER) database [7], propensity score-matched analysis suggested that the prognosis of ovarian SCC is worse than that of ovarian serous carcinoma. In an analysis of the prognostic predictors for patients with ovarian SCC, radiotherapy was associated with worse cause-specific survival. Although SCC generally shows a good response to radiotherapy, a systematic review did not support the efficacy of postoperative radiotherapy for ovarian SCC [8]. Thus, maximal reduction surgery is the standard treatment for ovarian SCC followed by postoperative chemotherapy of choice for typical epithelial ovarian cancer. A combination of platinum and taxanes as the standard chemotherapy for epithelial ovarian cancer has been used for ovarian SCC [9, 10], and the combi-

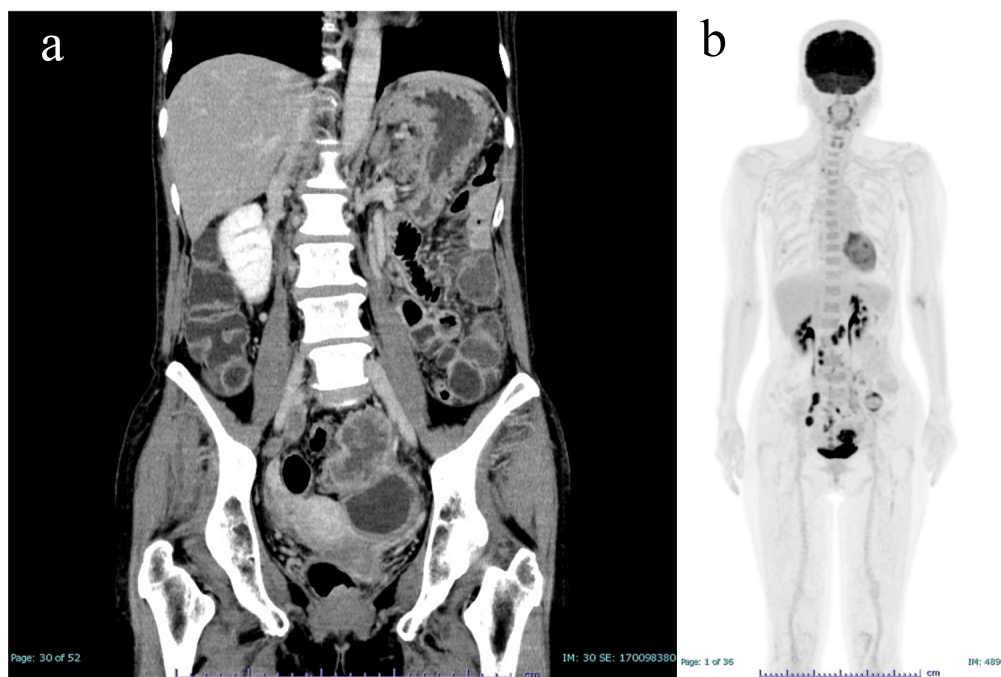


FIGURE 1. Radiological assessments of the ovarian tumor. (a) Computed tomography scan before the first surgery shows an ovarian tumor with cystic and solid areas present on the left side of the uterus. (b) Positron emission tomography-computed tomography image shows increased uptake of $[^{18}\text{F}]$ fluoro-2-deoxy-d-glucose in the para-aortic lymph nodes and residual tumor in the pelvis.

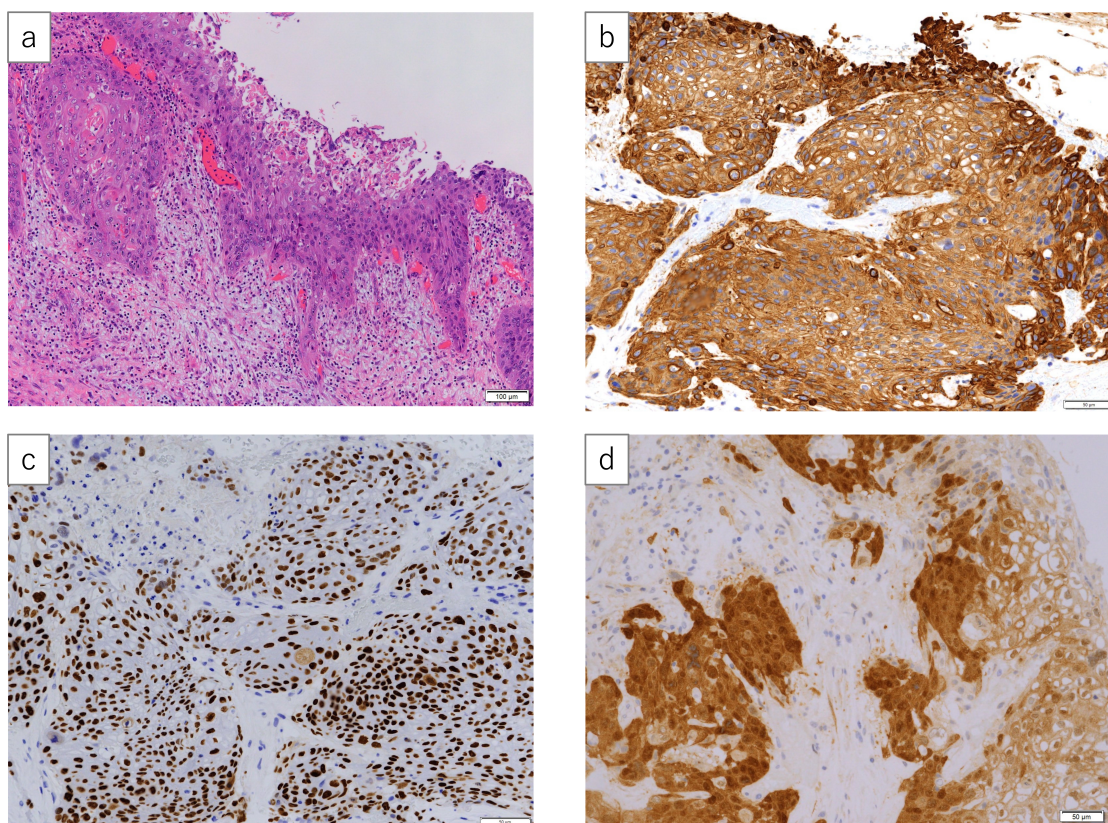


FIGURE 2. Histopathological findings of the first operative specimen of the left ovary. (a) Hematoxylin and eosin-stained section (magnification: $100\times$); (b) CK5/6 (magnification: $400\times$); (c) p40 (magnification: $400\times$); (d) p16 (magnification: $400\times$).

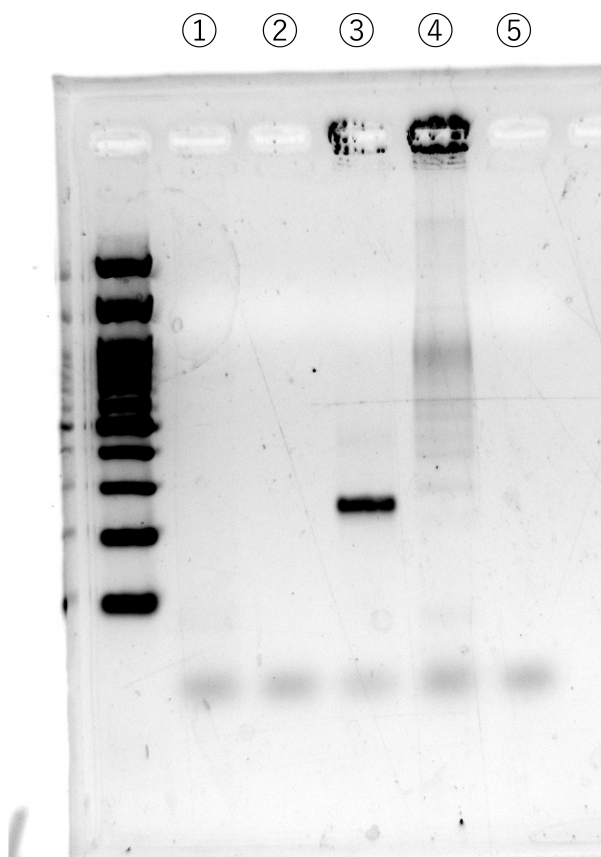


FIGURE 3. Polymerase chain reaction amplification of HPV from paraffin block samples of the initial surgical specimen. ① This case; ②–④ positive controls of cervical cancer with possible HPV infection; ⑤ negative control. HPV: human papillomavirus.

nation with a platinum regimen was associated with a better prognosis compared to other drugs [11].

HRD status predicts the efficacy of platinum-based chemotherapy in epithelial ovarian cancer and is an indicator of whether maintenance therapy with poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors is indicated. There are no reports on HRD-positivity rates in ovarian SCC; however, some reports have documented HRD-positivity in cutaneous SCC and lung SCC and the possible efficacy of PARP inhibitors [12, 13]. Thus, HRD status may be irrelevant in a certain number of HRD-positive SCCs.

With the advent of targeted therapies, including anti-vascular endothelial growth factor agents (bevacizumab) [14] and PARP inhibitors (olaparib, niraparib) [15, 16], HRD testing is used for selecting treatment for advanced ovarian cancer. Patients with HRD-positive advanced ovarian cancer have an improved prognosis when treated with first-line standard therapy comprising paclitaxel and carboplatin including bevacizumab, with the addition of maintenance therapy with olaparib [17]. In addition, a subgroup analysis revealed an impressive 89.7% 2-year progression-free survival rate when patients in the lower-risk group (stage III with upfront surgery and no residual disease) were treated with this regimen [18].

The residual dissemination in our patient was confined to

the pelvis, and lymph node metastasis was limited to the para-aortic lymph nodes below the renal vein. We were able to perform complete debulking surgery and there was no residual tumor larger than 1 cm. In addition, postoperative complications were minimal, allowing for a smooth transition to adjuvant chemotherapy. Bevacizumab was considered but was not administered because of the risk of anastomotic complications due to resection of the bowel and ureter. Therefore, we opted for niraparib alone for maintenance therapy after the completion of standard chemotherapy. Our results underline the importance of complete resection of refractory pure primary ovarian SCC because maintenance therapy with niraparib alone achieved a recurrence-free survival of more than 1 year after this surgery.

4. Conclusions

We presented a case of complete resection of advanced-stage pure primary ovarian SCC with HRD-positivity. Postoperative platinum-based chemotherapy and PARP inhibitors resulted in recurrence-free survival of more than one year after surgery. It is undeniable that complete resection of pure primary ovarian SCC at primary surgery, as in other epithelial ovarian cancers, is associated with improved prognosis. With the accumulation of more cases and elucidation of pathomechanisms and biomarkers, the prognosis of pure primary ovarian SCC is

expected to improve as postoperative drug treatment options are expanded.

AVAILABILITY OF DATA AND MATERIALS

The datasets supporting the conclusions of this article are included within the article (and its additional files).

AUTHOR CONTRIBUTIONS

KO and MK—wrote the main manuscript body. TN, YI and ToS—were responsible for pathological evaluation. TaS—performed the PCR analysis of HPV testing. TO and SY—read the article and gave the first author suggestions to improve the manuscript. All authors contributed to additional changes in the manuscript. All authors read and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This case report was approved by the Institutional Review Board of Hyogo Cancer Center (Approval No. G-330). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

ACKNOWLEDGMENT

We thank Enago (<https://www.enago.com/>) for editing a draft of this manuscript.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Keisuke Ogimoto, Miho Kitai, Takehito Ota, Takaaki Nakanishi, Yukihiro Imai, Toshiko Sakuma, *et al.* Pure primary ovarian squamous cell carcinoma with homologous recombination deficiency: a case report. *European Journal of Gynaecological Oncology*. 2024; 45(2): 158-162. doi: 10.22514/ejgo.2024.038.