

Recurrent uterine serous carcinoma with a germline pathogenic *BRCA2* variant treated using olaparib: A case report

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ABSTRACT

A germline pathogenic variant in *BRCA2* was secondarily found through genomic sequencing of uterine serous carcinoma. Clinical response to olaparib was observed in recurrent uterine serous carcinoma with a germline *BRCA2* mutation. Here, we report, for the first time, a long-term clinical response to olaparib in a patient with uterine serous carcinoma and a germline pathogenic *BRCA2* variant.

1. Introduction

Case report

A 57-year-old, Japanese woman (gravida 2) presented to our hospital with postmenopausal vaginal bleeding. She had no past medical or family history, and had a body mass index of 25.7 kg/m². Endometrial biopsy revealed the presence of a serous carcinoma. Pelvic magnetic resonance imaging (MRI) revealed a tumor invading the cervix and lower uterine segment (Fig. 1-A). ¹⁸F-fluoro-deoxyglucose positron emission tomography (FDG-PET) / computed tomography (CT) findings suggested a tumor in the lower uterine segment and multiple metastases to the pelvic lymph nodes. Complete cytoreduction was achieved by total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and retroperitoneal lymphadenectomy. The final pathologic diagnosis was uterine serous carcinoma stage IIIC1, according to the International Federation of Gynecology and Obstetrics (FIGO) staging for uterine cancer (2008). The tumor was 5 cm in diameter located in the lower uterine segment. There was no lymphovascular invasion, and less than half the myometrium appeared to have been invaded (Figs. 2 and 3). Metastases were found in the right ovary, pelvic lymph nodes, and the peritoneum of the Douglas pouch. The tumor in the right ovary was microscopic, and the tumor in the uterus and right ovary showed positivity for immunohistochemical staining of WT-1 (Fig. 2). There were no findings indicative of malignancy in the right fallopian tube and left adnexa.

The patient underwent six cycles of adjuvant chemotherapy with paclitaxel, carboplatin, and bevacizumab. She remained disease-free for 10 months after the completion of chemotherapy, at which point she complained of upper abdominal pain. FDG-PET/CT findings suggested

tumor recurrence in the peritoneum under the right diaphragm and the greater omentum (Fig. 1-B). A multi-gene panel examination of the tumor obtained from the primary surgery was performed via next-generation sequencing. The results revealed a *BRCA2* loss-of-function mutation (p.L1859fs, c.5576_5579delTTAA). After the patient and family members underwent genetic counseling, germline testing was conducted, and the same mutation was detected in the patient's germline cells.

While waiting for the above-mentioned genetic test results, the patient underwent second-line chemotherapy with doxorubicin and cisplatin. After two cycles of chemotherapy, the patient's serum CA125 level decreased from 397 to 201 IU/mL. FDG-PET/CT revealed a significant reduction in peritoneal dissemination and decreased maximum standardized uptake (SUVmax from 10.1 to 3.4) in the recurrent tumors (Fig. 1-C). The recurrent tumors were found to be platinum sensitive, but chemotherapy was halted due to ileus that occurred each time after cisplatin administration and for which hospitalization was required.

Due to limited therapeutic options and the somatic and germline *BRCA2* mutations, olaparib was considered as a candidate for treatment. A multidisciplinary team conference was held, and institutional review board approval was granted. Informed consent was obtained from the patient and her family, and off-label use of olaparib was chosen as the treatment plan, though the treatment was not covered by medical insurance. Olaparib was administered orally (300 mg twice daily, a total daily dose of 600 mg). The patient was relieved of the abdominal pain after being treated with olaparib for 3 months, and her serum CA125 level decreased to 26.6 IU/mL. However, she also experienced anemia, which is an adverse effect of olaparib; thus, intermittent cessations and several rounds of blood transfusion were

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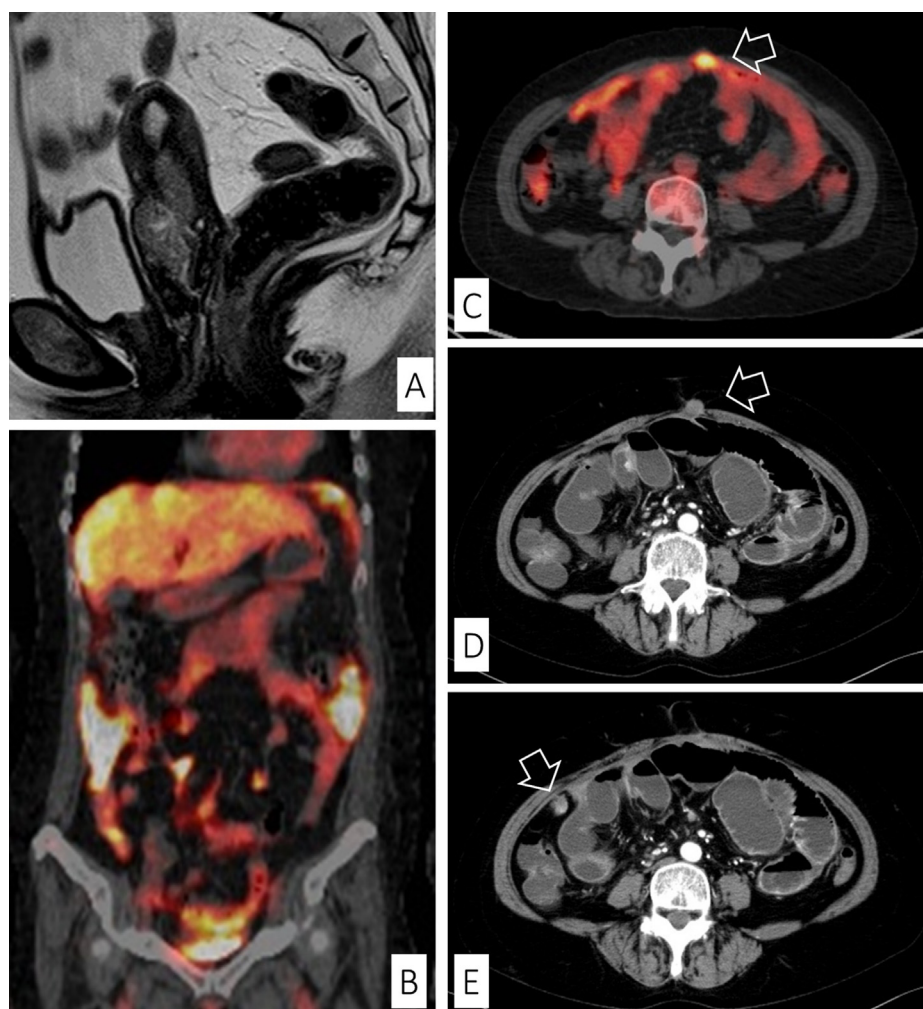


Fig. 1. A: Magnetic resonance image (T2 image) acquired before the primary surgery. The tumor was located in the lower uterine segment and cervix. B: ^{18}F -fluoro-deoxyglucose positron emission tomography (FDG-PET)/ computed tomography (CT) performed after first-line chemotherapy for the diagnosis of recurrence. Peritoneal dissemination in multiple sites, and strong accumulation of FDG in the lesions under the right diaphragm and in the greater omentum and parietal peritoneum can be observed. C: FDG-PET/CT after two cycles of second-line chemotherapy showing a significant reduction in peritoneal dissemination and decreased accumulation of FDG. D and E: Enhanced CT performed 11 months after olaparib initiation showing peritoneal dissemination in the abdominal wall and small bowel obstruction. The arrow in panel D indicates the lesion seen in panel C; this lesion became slightly larger after 11-month treatment with olaparib. The arrow in panel E shows one of the new peritoneal dissemination lesions.

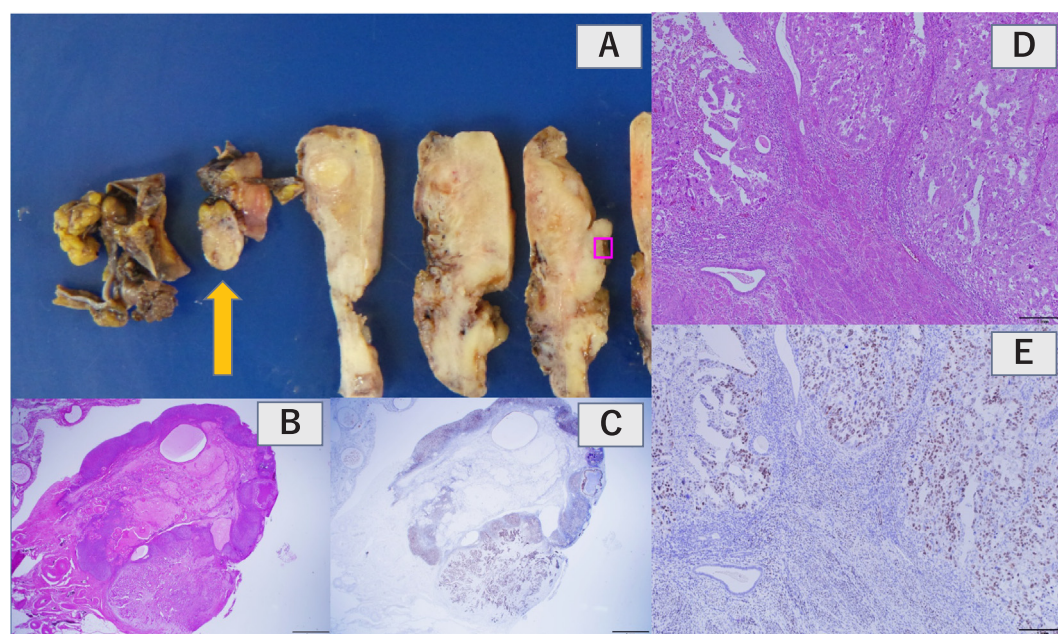


Fig. 2. A: Macroscopic findings of the uterus and adnexa obtained from the primary surgery. The uterus and cervix were cut through the midline and a parallel axis. The tumor was 5 cm in diameter and was located in the lower uterine segment. The arrows show the normal-sized and macroscopically normal ovaries. B and C: Loupe view of the right ovary shows 4×5 mm and 1×1 tumors. B: Hematoxylin and eosin (H&E) staining. C: Immunohistochemical staining of WT-1. The tumors show positivity for WT-1. D and E: Tumor in the uterus. D: H&E staining. E: Tumor cells are positive for WT-1.

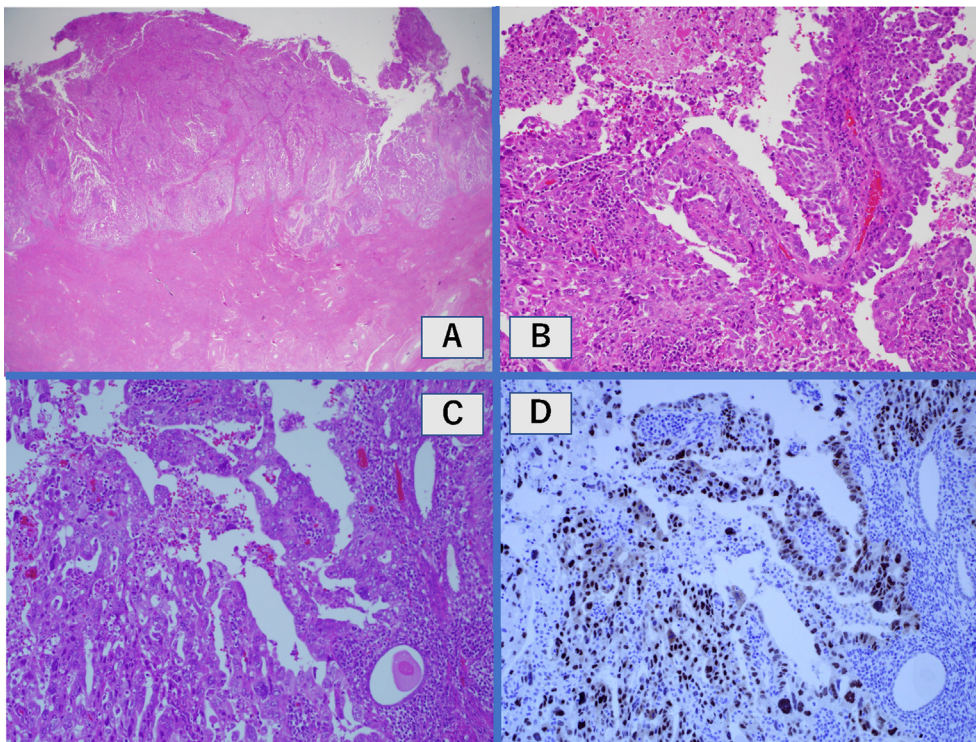


Fig. 3. Histological findings of the uterus: hematoxylin and eosin staining (A, B, and C) and immunohistochemical staining for p53 (D). A: Tumor cells were observed mainly in the surface of the endometrium. B: Papillary growth of tumor cells with high-grade cellular and nuclear atypia. C: Coexistence of tumor cells on the left and residual non-neoplastic atrophic glands on the right; these findings suggest that tumors developed from the non-neoplastic atrophic endometrial glands and grew replacing the non-neoplastic glands. D: Serous carcinoma with strong and diffuse positivity for p53, and non-neoplastic endometrial glands negative for p53. These findings are consistent with high-grade serous carcinoma of the uterus origin.

required. The dosage of olaparib was reduced to two daily doses of 200 mg (for a total daily dose of 400 mg). Subsequently, the patient's appetite recovered, and she became free of pain. Olaparib was administered for another 8 months, during which the patient remained asymptomatic. The patient developed bowel obstruction during taking olaparib, thus olaparib was discontinued. The placement of an ileus tube was ineffective in treating bowel obstruction. Enhanced CT showed pelvic peritoneal dissemination without masses or ascites (Fig. 1-D and E). The patient decided to discontinue olaparib and other anticancer treatments. The patient has since been receiving total parenteral nutrition and supportive care at home; at the time of writing this report, the patient has been alive at home for two months with disease.

Written informed consent to report the case was obtained from the patient.

2. Discussion

Here, we report two new insights from a case of uterine serous carcinoma. First, a *BRCA2* pathogenic variant was secondarily identified via genomic sequencing of uterine serous carcinoma. Second, we report the long-term clinical response of a patient treated with olaparib for 11 months. Considering that there are limited standard chemotherapeutic options for recurrent endometrial cancer, and hormonal therapy is not effective for uterine serous carcinoma, our patient underwent tumor DNA sequencing to identify possible targeted treatments. The results of the somatic tumor panel led to a secondary finding of a germline *BRCA2* mutation. The patient had no family or medical history of cancer, and the *BRCA2* mutation was unexpected.

It remains unclear whether mutations in *BRCA1* and *BRCA2* are associated with increased risks for endometrial cancer, and especially uterine serous carcinoma. A case-controlled study found no differences in risks of endometrial cancer between individuals with and without *BRCA1/2* mutations (Segev et al., 2015). In contrast, studies show that patients with *BRCA1* mutations undergoing risk-reducing salpingo-oophorectomy have increased risks of uterine serous carcinoma (Shu et al., 2016; Saule et al., 2018).

Conversely, the frequency of *BRCA1/2* mutations has been reported to be higher among patients with uterine serous carcinoma than among those with all histologic types of endometrial cancer. A different study reported that among unselected 381 endometrial cancer patients who underwent cancer panel testing, 26 had serous carcinoma, and among them *BRCA2* mutations were found in one patient with uterine serous carcinoma. A *BRCA1* mutation was found in one of 289 patients with endometrioid carcinoma (Ring et al., 2016). A meta-analysis demonstrated three out of 207 Caucasian women with uterine serous carcinoma had germline *BRCA1/2* mutations (Jonge et al., 2017). Accordingly, it is estimated that 1–3% of uterine serous carcinomas are associated with *BRCA1/2* mutations.

Olaparib, the first poly (ADP-Ribose) polymerase (PARP) inhibitor, was approved by the Food and Drug Administration for the treatment of recurrent platinum-sensitive ovarian cancer with germline or somatic pathogenic *BRCA1/2* mutations and also for patients with germline *BRCA*-positive, HER2-negative metastatic breast cancer. The efficacy of olaparib for the treatment of patients with metastatic pancreatic cancer with *BRCA1/2* mutations was demonstrated in a randomized-controlled trial (Golan et al., 2019). Olaparib also showed positive phase III results in metastatic prostate cancer treatment.

The efficacy of olaparib in endometrial cancer patients with germline *BRCA1/2* mutations remains unknown. To our knowledge, there has only been one case report showing a durable response (more than 15 months) to olaparib treatment in a patient with recurrent grade 1 endometrioid carcinoma with a germline *BRCA2* mutation and a different somatic *BRCA2* mutation (Gockley et al., 2018). This case report was the first to show a 11-month clinical response to olaparib in a patient with uterine serous carcinoma with a germline pathogenic *BRCA2* variant.

It also remains unclear whether uterine serous carcinoma is a manifestation of homologous recombination deficiency (HRD). Previous work has suggested that HRD and sensitivity to PARP inhibitors were tied to *BRCA*-associated cancer types in patients with *BRCA1/2* mutations (Jonsson et al., 2019). Jonge et al. showed HRD occurs in high-grade, non-endometrioid endometrial cancers (serous carcinoma and carcinosarcoma) and is related with pathogenic *BRCA1*

variants or high somatic copy-number losses of HR genes. In their study, 24% ($n = 6$) of endometrial cancers were HR deficient, with either serous carcinoma or carcinosarcoma with a serous component, and two of them had pathogenic *BRCA1* variants (Jonge et al., 2019a). In addition, Jonge et al. also reported that, among 40 endometrial cancer patients with germline *BRCA1/2* mutations, there were six with uterine serous carcinoma (3 *BRCA1* and 3 *BRCA2* mutations), five of whom were positive for loss of heterozygosity of the *BRCA1/2* wild-type allele (3 *BRCA1* and 2 *BRCA2* mutations). They thus suggested that endometrial carcinoma might be a form of germline *BRCA*-associated hereditary breast and ovarian cancer (Jonge et al., 2019b).

Although the frequency of germline *BRCA1/2* mutations in patients with uterine serous carcinoma may not be high, olaparib could be an efficient treatment strategy for uterine serous carcinoma in cases involving HRD or germline *BRCA1/2* mutations. Finally, screening for germline *BRCA1/2* mutations may be worthwhile.

In summary, olaparib provided 11-month progression free survival for the patient in our case report. Our report suggests that uterine serous carcinoma may be a *BRCA*-associated cancer. Germline or tumor DNA testing for pathogenic *BRCA1/2* mutations in patients with uterine serous carcinoma might be beneficial, and olaparib could be a potential treatment option in patients with a germline pathogenic *BRCA2* variant.

3. Conclusion

Olaparib could be a promising candidate for the treatment of uterine serous carcinoma associated with germline *BRCA2* mutations.

Author contributions

Kayo Inoue drafted the article, Hisroshi Tsubamoto supervised, Tomoko Ueda and Chihiro Tajima collected information, and Nami Nakagomi drafted the pathological information and selected the figures. All authors read and approved the final article.

Statement of informed consent

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.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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