

CASE REPORT

Recurrence of low-grade serous ovarian cancer successfully treated with Gemcitabine and Bevacizumab: a case report and literature review

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Abstract

Ovarian low-grade serous carcinoma (LGSC) is usually a slow growing tumor with a relatively good prognosis. However, LGSC that have relapsed are highly resistant to chemotherapy, and there is currently no established treatment for them in contrast to high-grade serous carcinoma (HGSC). Here, we first review the literature on this topic and then describe a case of LGSC that relapsed and responded to Gemcitabine and Bevacizumab. The patient was a 37-year-old nulliparous woman who had undergone three cycles of topotecan after initial surgery at age 28.5 years as well as three months later during a disease-free interval. Intraperitoneal dissemination was observed and laparoscopic biopsy was performed. Histopathological examination revealed LGSC, and genetic testing revealed mutations in the *neurofibromatosis type 1 (NF1)* and *TP53* genes. The mass of the disseminated lesion subsequently increased overall, and subileus was observed. The patient was treated, but the operation was incomplete. Postoperatively, Gemcitabine and Bevacizumab therapy was started. After six cycles, tumor markers became negative and Positron Emission Tomography-CT (PET-CT) showed decreased tumor activity. There were 20 cycles without any symptoms. LGSC is often resistant to anticancer drugs, but Gemcitabine and Bevacizumab therapy was able to suppress the lesions and symptoms in this case. With these findings, future genomic testing may assist in the treatment strategy for cases of LGSC recurrence, which are considered to be less likely to respond to anticancer drugs. Comprehensive genetic analysis will hopefully lead to the molecular mechanism of carcinogenesis for more effective and targeted therapies.

Keywords

Ovarian cancer; Low-grade serous carcinoma; Gemcitabine; Bevacizumab; Genetic mutation

1. Introduction

Low-grade serous carcinoma (LGSC) in ovarian cancer is fairly rare and characterized by a relatively young age of onset (early 40s); it accounts for 2% of epithelial ovarian cancers and 4–5% of serous cancers [1–3]. Versus high-grade serous carcinoma (HGSC), which is often detected in advanced stages of cancer, LGSC is often confined to the ovary at diagnosis and progresses more slowly; it has a better prognosis than HGSC [4]. Johns Hopkins University has classified ovarian tumors into Type 1 and Type 2 based on the molecular mechanism of carcinogenesis with LGSC being Type 1 and HGSC as Type 2 [5]. A 2014 revision of the World Health Organization (WHO) classification of ovarian tumors (4th edition) classified ovarian serous adenocarcinomas into low and high atypia [6]. In other words, LGSC is a new concept classified in recent years. Type 1 develops in stages through pre-cancerous lesions

such as benign tumors and borderline malignancies. Type 2 HGSC originates from serous tubal carcinoma in situ (STIC) of the fallopian tube sheath. Whole exome sequencing has been performed on each of these tumors, and the genetic mutations described below have been identified [4].

LGSC is usually a slow growing tumor with a relatively good prognosis. However, LGSC is highly resistant to chemotherapy, and there is currently no established treatment for LGSC in contrast to HGSC [7, 8]. Therefore, the ability to achieve complete surgical removal is important not only in cases of initial disease but also in cases of recurrence; the prognosis is greatly influenced by the outcome [9].

In this study, we experienced a case of recurrence 5 years after initial surgery, in which secondary debulking surgery (SDS) failed to completely resect the tumor, and postoperative chemotherapy (gemcitabine and bevacizumab) was used to control the lesion and symptoms. Gemcitabine is an older drug

classified as a pyrimidine antagonist. It works by entering the DNA of cancer cells and inhibiting the synthesis of DNA necessary for cell division, thereby eliminating cancer cells and suppressing cancer division and growth. Bevacizumab is a recombinant humanized monoclonal antibody against human vascular endothelial growth factor (VEGF), which inhibits angiogenesis in tumor tissue by blocking the biological activity of VEGF, thereby inhibiting tumor growth.

We report our experience with postoperative chemotherapy (gemcitabine and bevacizumab) in relapsed LGSC, with a review of the literature.

2. Methods

We conducted a literature search using a Medical Literature Analysis and Retrieval System On-Line (MEDLINE) search and Web of science (May 2022). The keyword was “low-grade serous carcinoma”, and the search range was 1970 to 2020. We selected reports describing the use of Bevacizumab and Gemcitabine. We will also include a case report from our experience.

In this case, a laparoscopic biopsy was also performed. Informed consent was obtained from the patient for the tissue obtained from the biopsy, and the usual histopathological examination was performed, and the tissue was used for cancer gene panel testing using FoundationOne® CDx.

3. Results

3.1 Case report

The patient was a 37-year-old nulliparous woman who underwent right adnexectomy and partial omentectomy for a 10-cm ovarian tumor at age 28; the tumor was suspected to be a borderline malignant tumor at another hospital. A postoperative histopathological examination revealed a serous borderline malignant tumor with invasive peritoneal implants. She was referred to our hospital for close examination and treatment with carboplatin and paclitaxel for three cycles. After completion of chemotherapy (4 months after surgery), recurrence was found in the left ovary, and thus a simple total hysterectomy, left adnexectomy, subtotal omentectomy, as well as pelvic and para-aortic lymph node dissection were performed. Postoperative histopathology revealed advanced low-grade serous carcinoma (stage IIIC; Fig. 1).

The patient had a platinum-resistant recurrence and doxorubicin hydrochloride was started, but was later discontinued due to anaphylactic shock at the first dose. The patient was then switched to topotecan for three cycles. Computed tomography (CT) showed intra-abdominal seeding after 5 years and 3 months without disease. The intra-abdominal seeding lesions were 1.5 cm in size around the spleen, 1 cm in size in the left paracolon area, and 1.2 cm in size in the mesenteric midline. A laparoscopic biopsy was performed on the area. The biopsied histopathology was diagnostic of LGSC. Genetic examination of the biopsy tissue revealed *neurofibromatosis type 1 (NF1)* and *TP53* genetic mutations. Microsatellites were stable, and the loss of heterozygosity (LOH) score was 0.9%. Although complete resection of the intra-abdominal seeding lesion had

not been achieved, the patient was placed on a policy of observation because there were no symptoms in this case.

Six months later, CT showed that the tumor in the mesenteric midline had increased to 3 cm in size with calcification. A new tumor 3 cm in size also appeared in the median pelvic region. Other intra-abdominal seeding lesions of 1 cm in size were present in nine other locations on the images. Six months later, CT showed that the mesenteric midline tumor had increased to 5.5 cm in size and the median pelvic region had increased to 5.2 cm in size. Other intra-abdominal seeding lesions were also enlarged to 2–3 cm in size, and almost all of the tumors were accompanied by calcification. Six months later (1 year and 6 months after the laparoscopic biopsy), CT showed that the largest mesenteric midline tumor had become a mass 10 cm in diameter, and the median pelvic region was 7.5 cm in size. Other intra-abdominal seeding lesions were also enlarged, ranging from 2 to 4 cm in size. At that time, the patient was associated subileus, and the decision was made to perform surgery. The tumor was tightly adherent to the small intestine in multiple locations, and thus complete removal would have left only a nonfunctional length of the small intestine; thus, there was incomplete surgery with removal of only the largest mesenteric midline tumor (Fig. 2). Postoperative Gemcitabine and Bevacizumab therapy (Day 1 Gemcitabine 1000 mg/m², Bevacizumab 15 mg/kg, Day 8 Gemcitabine 1000 mg/m², 21-day cycle) was started. After six cycles, cancer antigen125 (CA125) decreased from a peak of 145 IU/mL to 17 IU/mL in the normal range (Table 1).

Seven months after surgery, CT showed a 7.5 cm tumor in the median pelvis with calcified areas and a tumor 7.5 cm in size, which was judged to be SD. But eleven months after surgery, Positron Emission Tomography-CT (PET-CT) showed decreased ¹⁸F-fluorodeoxyglucose (FDG) accumulation (standardized uptake value (SUV) max decreased from 10.5 before surgery to 7.6) (Fig. 3). PET-CT taken 1 year and 5 months after surgery showed a decrease in FDG accumulation (SUVmax decreased from 7.6 to 6.1 in the previous study), although the tumor size remained the same with calcification. The patient is currently receiving 20 cycles of Gemcitabine and Bevacizumab therapy, and symptoms such as ileus have resolved with no side effects; it has now been nine years and two months since the initial onset and three years since the relapse.

3.2 Literature review

A MEDLINE search identified 958 articles on ovarian low-grade serous carcinoma. The search for Bevacizumab led to 17 articles. The search for Gemcitabine led to four articles. A Web of Science search resulted in 1151 articles on ovarian low-grade serous carcinoma. Of these, 26 papers were found for Bevacizumab with three for Gemcitabine. A total of 50 cases were reviewed, and four cases of ovarian low-grade serous carcinoma treated with either Bevacizumab or Gemcitabine were reported [10–13].

Dalton *et al.* [10] reported an overall response rate (complete response (CR) + partial response (PR)) of 47.5% for Bevacizumab containing regimens in 40 patients. Two of these patients were treated with Bevacizumab and Gemcitabine

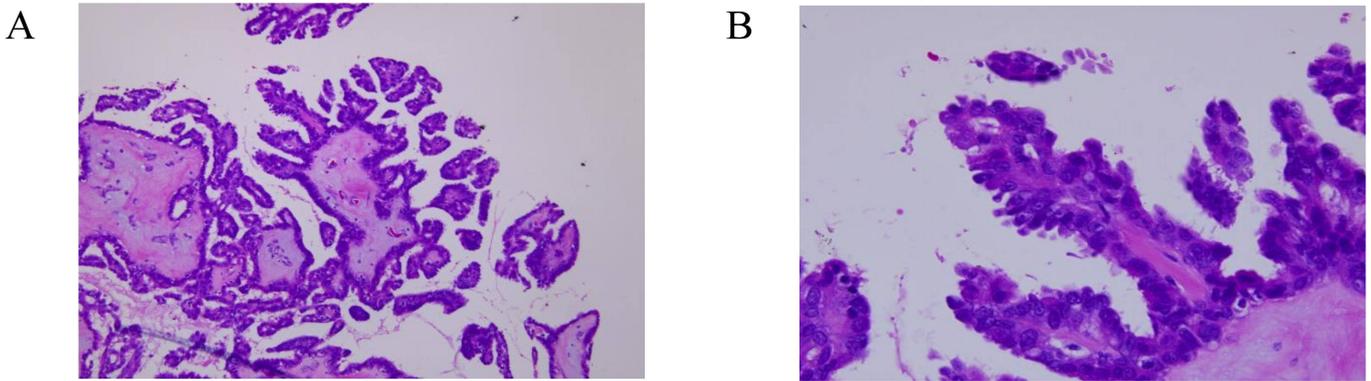


FIGURE 1. Postoperative Histopathology. Diagnosis of low-grade serous carcinoma. (A) Hematoxylin-Eosin (×40). (B) Hematoxylin-Eosin (×400).

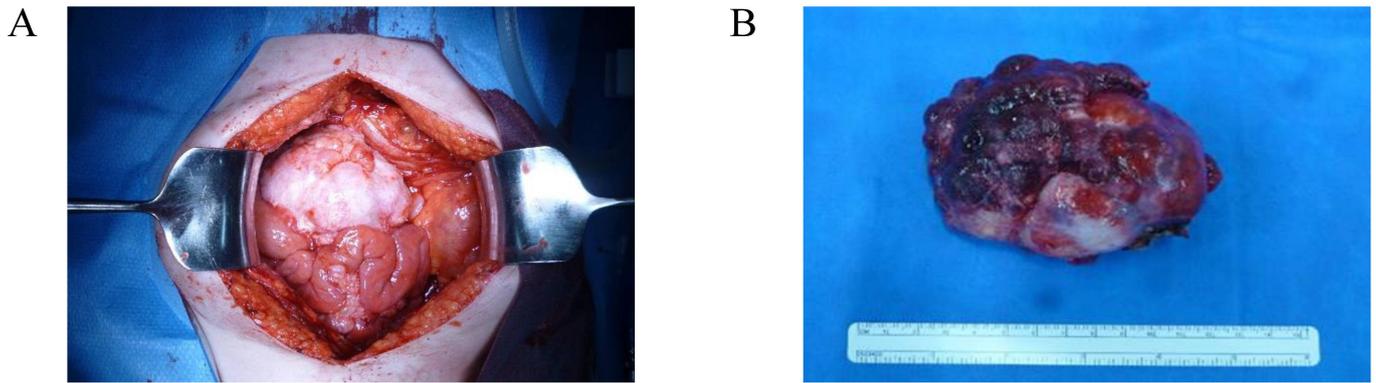


FIGURE 2. Intraoperative Photographs. (A) Intraoperative Finding. (B) Excised Sample.

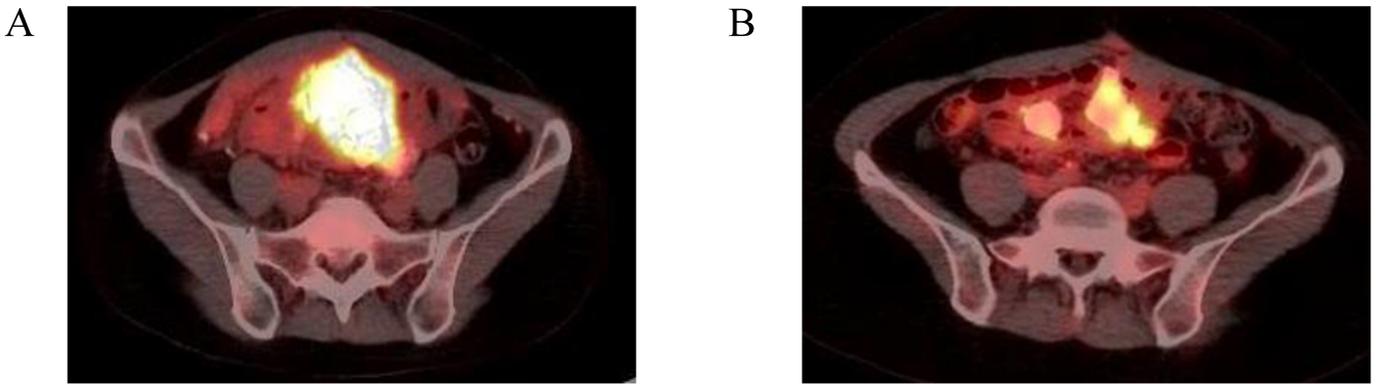


FIGURE 3. PET-CT findings. (A) Before tumor removal. (B) The same area after 18 cycles of Gem + Bev therapy.

TABLE 1. Changes in tumor markers (CA125) with treatment.

	initial medical examination (28yo)	TAH + BSO (29yo)	laparoscopic biopsy (34yo)	Tumortectomy (35yo)	Gem + Bev 2cycle (36yo)	Gem + Bev 4cycle (36yo)	Gem + Bev 6cycle (36yo)	Gem + Bev 12cycle (37yo)	Gem + Bev 20cycle (37yo)
CA125 (U/mL)	45	13	67	145	56	31	19	20	22

CA: cancer antigen; Gem: Gemcitabine; Bev: Bevacizumab; yo: years old.

similar to this case; both had progressive disease (PD). Grisham *et al.* [11] reported that among ten patients with ovarian low-grade serous carcinoma, five had PR with a regimen of Bevacizumab in combination with chemotherapy including one patient who received Bevacizumab and Gemcitabine as in this case. Rose *et al.* [12] reported only 1 of 12 patients (8.3%) treated with Bevacizumab alone had a response. A case report included patients treated with Cyclophosphamide and Bevacizumab for more than seven years [13].

4. Discussion

Ovarian LGSC has a better prognosis than HGSC. However, the prognosis is worse for patients with stage II or higher disease or recurrent disease as in this case. The rationale is that LGSC is much less sensitive to anticancer agents than HGSC. Therefore, as with HGSC, primary debulking surgery (PDS) is required to achieve R0 (no macroscopic residual tumor) in the initial treatment [9]. Those with more than 1 cm residual tumors have a lower disease-free survival and overall survival rate than those with less than 1 cm of residual tumors [14]. Thus, more than 70% of stage III–IV LGSC will likely recur. However, in cases of recurrence, as in this case, we recommend to resect as much of the lesion as possible preferably with SDS [8, 15]. However, patients who do not achieve R0 are eligible for chemotherapy, but this treatment has a very low response rate of about 5% [2, 8].

Stable disease (SD) accounts for 60.2% of all cases, and a certain level of efficacy has been observed. There is no specific regimen for LGSC, and platinum-based anticancer agents are often used as in the case of HGSC [7]. Here, the patient was judged to have platinum-resistant recurrence, and Gemcitabine was selected as in the usual treatment for recurrence of ovarian cancer. Bevacizumab and other angiogenesis inhibitors have shown some efficacy [10, 11], but Bevacizumab and Gemcitabine therapy is currently reported in only three cases to the best of our knowledge: one PR and two PD [10, 11]. However, the reports to date have been from a single hospital. The number of cases is low, and thus the evidence is still insufficient. Hormonal therapies such as aromatase inhibitors, tamoxifen, and gonadotropin releasing hormone (GnRH) agonist therapy are also sometimes effective. The response rate for these therapies is about 10%, but SD is seen in about 50% of cases indicating some efficacy [16, 17]. Thus, these can be an option in cases that are unresponsive to other treatments.

Kirsten rat sarcoma viral oncogene homolog (*KRAS*) and *BRAF* mutations are found in 30–70% of LGSC, but *TP53* mutations are usually absent [1, 18]. These genes are thought to be involved in the activation of the Mitogen-activated Protein Kinase (MAPK) signaling pathway and contribute to the proliferation and invasion of LGSC. The mutation rate of the MAPK pathway is estimated to occur in about 40% of cases [19]. Therefore, Selumetinib, which inhibits MEK1/2 involved in this pathway, has shown some efficacy in clinical trials [20]. However, the importance of next-generation sequencing (NGS) for targeted therapy is not adequately demonstrated and should be considered in the future. On the other hand, LGSC in Asian patients has few *KRAS* or *BRAF* gene abnor-

malities; Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform (*PIK3CA*) mutations are more common [21, 22]. This case had no *KRAS* or *BRAF* gene abnormalities; mutations in *NF1* and *TP53* were observed. The LOH score was 0.9%, however, and the patient was considered to have LGSC when combined with pathological examinations.

In this case, we experienced a recurrence of LGSC, which is considered to be resistant to anticancer drugs. SDS was attempted, but the majority of the tumor remained. Nevertheless, the tumor accumulation decreased, and the tumor markers became negative. The reason for the successful treatment in this case may be the presence of a *TP53* mutation, which has not yet been reported in LGSC before. There are also reports that the angiogenesis inhibitor Bevacizumab has some efficacy, which may also be a factor. However, LGSC is a rare tumor, and thus there is still a lack of information about this disease.

With these findings, future genomic testing may assist in the treatment strategy for cases of LGSC recurrence, which are considered to be less likely to respond to anticancer drugs. Comprehensive genetic analysis will hopefully lead to the molecular mechanism of carcinogenesis for more effective and targeted therapies.

AUTHOR CONTRIBUTIONS

HS and YK—were major contributors in writing the article. HS, YK, TY, KM and HN—made clinical examinations, performed surgery and chemotherapy. CM and TO—made with pathological diagnosis. NM—supervised the project. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Institutional Review Board of Kindai University Faculty of Medicine has confirmed that Ethics Board approval is not required for case reports of nine or fewer cases. Therefore, the ethics approval is not applicable to this case report. Informed consent was obtained from the patient for this case, and the patient consented to its publication.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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