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Invasive Low-grade Serous Ovarian Carcinoma: Small Case Series

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Abstract

Background: Low-grade serous ovarian carcinoma (LSSOC) is the rare histological type of epithelial ovarian cancer and accounts for 5% to 10% of serous ovarian cancers and 6% to 8% of all ovarian cancers. LGSOC is known to be resistant to conventional cytotoxic chemotherapy. LGSOC in about 70% of cases diagnosed at an advanced stage (FIGO III-IV). These neoplasms have less aggressive biological behavior than high-grade serous ovarian cancer; however, over 80% of patients will experience disease recurrence. This study aims to review histology and assess the volume of LGSOC and the invasive implants and correlate these findings with clinical presentation, outcome, and management.

Methods: Our study presents a case series of five patients diagnosed with low-grade serous ovarian carcinoma, including one with borderline serous ovarian tumor with invasive implants (2003). All patients underwent cytoreductive surgery and adjuvant chemotherapy. Two of these patients also received endocrine therapy. We have described each case in detail and provided a review of a borderline serous tumor and low-grade serous carcinoma.

Results: We report four low-grade serous ovarian carcinoma cases and one case of a serous borderline ovarian tumor with invasive implants, a total of five patients. The age of the patients was between 28 to 60 years. Three patients (60%) underwent initial surgery with curative intent. Chemotherapy was given to four patients (80%), and two individuals (40%) received both neoadjuvant and adjuvant chemotherapy. Endocrine therapy was given to two individuals (40%) in addition to chemotherapy. Within three months of surgery, one patient (20%) died. The average period of follow-up was 27 months.

Conclusion: Low-grade serous ovarian carcinoma is classically known to be chemo resistant. Thus, primary surgical treatment is the first-line therapy for LGSOC as well as for the recurrence of the disease. In first-line treatment based on the stage, the standard treatment includes cytoreductive surgery followed by platinum-based adjuvant chemotherapy. Hormone therapy is usually considered as a maintenance treatment after completing first-line treatment.

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Introduction

Epithelial ovarian cancer is also known as ovarian carcinoma and represents the most significant percentage of malignant ovarian tumors; and it is characterized by five histological subtypes: high-grade serous ovarian carcinoma (HGSOC; 70%), endometrioid carcinoma (ENOC; 10%), clear cell carcinoma (CCOC; 10%), low-grade serous ovarian carcinoma (LGSOC; <5%), and mucinous ovarian carcinoma (MOC; 3%) [1-3].

Serous ovarian carcinoma is the most common epithelial ovarian cancer and is subdivided into high-grade serous ovarian carcinoma (HGSOC) and low-grade serous ovarian carcinoma (LGSOC). LGSOC is responsible for approximately 5% of patients diagnosed with serous carcinoma of the ovary, and around 70% of LGSOCs are diagnosed at an advanced stage (FIGO III-IV). These neoplasms have less aggressive biological behavior and are less sensitive to chemotherapy than HGSOC. The median age at the diagnosis is 46.9, and an overall five-year survival rate is 54.2% [4,5]. Most of these patients exhibit a poor response rate to conventional chemotherapy and remain at risk of recurrence and cancer-related death. Therefore, it is imperative to identify invasive implants that classify borderline serous tumors as low-grade serous ovarian cancer. The volume of the invasive disease may have prognostic significance.

Clinical symptoms of LGSOC are similar to HGSOC and include abdominal or pelvic pain, bowel dysfunction, abdominal distention, and bladder dysfunction. The diagnosis of LGSOC includes a detailed history, clinical examination including a pelvic examination, CA 125, ultrasound of the abdomen and pelvis, or other imaging techniques such as computed tomography (CT) scan of the thorax, abdomen, and pelvis or whole-body magnetic resonance imaging (MRI) as CT and MRI to characterize the extent of disease and management [4,5].

Histologically LGSOC is represented by a monotonic proliferation of cuboid, low columnar cells, mild to moderate atypia without nuclear pleomorphism, mitotic index up to 12 mitoses per 10 high power fields (HPF), and destructive invasion [5]. LGSOC have KRAS and BRAF mutations in about two-thirds of cases and very rarely contain TP53 mutations. Moreover, LGSOC has a high expression of estrogen receptors (ERs) and progesterone receptors (PRs), making it sensitive to endocrine therapy [4,5].

The vast majority of LGSOCs are related to a serous borderline ovarian tumor (SBOT) displaying a micropapillary pattern [4,6].

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Approximately 2/3 of borderline tumors are limited to the ovary at the time of diagnosis. The remaining 25-35 percent of tumors display extra ovarian implants, which may vary in number and invasiveness. The current 2014 classification of tumors of the female genital organs has recently classified invasive implants of serous borderline tumors (SBT) as low-grade serous carcinoma (LGSC) as these lesions have aggressive biological behavior. The long-term outcome of ovarian SBT related to small foci of invasive peritoneal disease (LGSC) compared to primary ovarian/peritoneal LGSC with widespread peritoneal carcinomatosis is not clear.

The molecular mechanisms underlying the progression of borderline serous tumors to LGSC are not clear. Many studies have demonstrated abnormal activation of mitogen-activated protein kinase (MAPK) pathway (including mutation of two key components, KRAS exons 2-3 and BRAF) in approximately 50% of SBT and frequently LGSC. It is not known whether there are differences in KRAS and BRAF mutations in non-invasive and invasive extra ovarian implants or their prognostic significance. A few studies have suggested that BRAF mutation may be a protective factor for developing the more aggressive disease. These findings, if confirmed, may predict the risk of recurrence or progression in a given case of SBT and LGSOC.

Materials and Methods

The study was conducted at the University of Saskatchewan, Department of Obstetrics and Gynecology, Division of gynecologic oncology. The medical records of patients diagnosed with low-grade serous ovarian carcinoma and borderline serous ovarian tumor with invasive implants were reviewed in the Saskatchewan Health Region between July 2009 and December 2018.

Research Design/Data Collection

Retrospective data were collected on the study population, which consisted of females diagnosed with low-grade serous ovarian carcinoma or borderline tumors with invasive components between July 2009 and December 2018. The pathology database at Saskatchewan Health Region had been searched for "serous borderline tumors" and "Low-grade serous carcinoma." All eligible cases underwent pathology review by expert gynecological pathologists on a complete set of hematoxylin and eosin (H&E) stained slides. Five cases have been identified. Two 0.6 mm cores were removed and sent to the Molecular laboratory for KRAS, BRAF, and NRAS mutational analysis.

The following data were collected: age, diagnosis, body mass index, pernicious habits, and initial oncologic treatment (surgery, chemotherapy, or radiotherapy).

Case Description

In this report, we describe five cases (four low-grade serous ovarian carcinoma cases and one case of a borderline serous ovarian tumor with invasive implants); all underwent treatment at the Department of Obstetrics and Gynaecology at Saskatchewan Health Region (SHR) between 2009 and 2018.

Patient 1

This 38-year-old woman, G2P2 with BMI 25.2, presented with a pelvic mass, significant pain, and a small amount of ascites. She underwent diagnostic laparoscopy with a peritoneal biopsy in October 2015; some tumor nodules were noted in the pelvis during surgery. The pelvis otherwise appeared to be quite inflamed and scarred; thus, the only biopsy was taken. The pathology at the time of the frozen section reported serous carcinoma. The final histopathology was reported as a low-grade serous carcinoma in the background of a borderline serous tumor with invasive implants. The final stage was IIIC low-grade serous carcinoma with deep invasion. This patient received three cycles of neoadjuvant chemotherapy (combinations of carboplatin and Paclitaxel) and underwent interval debulking, including bowel resection, colostomy, and macroscopic residual, in December 2015. She completed three cycles of adjuvant chemotherapy with carboplatin/Paclitaxel and bevacizumab and received five cycles of bevacizumab as maintenance. However, the treatment was discontinued due to disease progression. During maintenance treatment, a large mass in the pouch of Douglas filling her lower pelvis as well as some nodularity in the anterior wall of the rectum was noted. The recurrence of the disease was confirmed in July 2016. She was admitted to the hospital, and consideration of secondary debulking was being discussed. The patient was deceased in the palliative care unit in April 2017.

Patient 2

This patient was 59 years old woman, G3P3 of BMI 30, who underwent primary surgery in April 2016 for a large left pelvic mass with elevated CA-125. The frozen section was reported as a serous borderline ovarian tumor. She also had right adnexal mass, deposits on the peritoneum, and colon that were reported as an invasive implant with low-grade serous carcinoma by frozen section. She underwent a hysterectomy, tumor debulking, omentectomy, and resection of the bowel. The final pathology was invasive serous carcinoma with a major desmoplastic reaction. The final stage was IIIC low-grade serous carcinoma. This patient received one cycle of adjuvant Carboplatin and Paclitaxel chemotherapy, but due to postoperative complications and rapid progression of cancer in the lungs, she deceased in 3 months after diagnosis.

Patient 3

The patient was 59 years old woman, G2P2 of BMI 20.4, who presented with a pelvic mass, abdominal pain, and discomfort. She underwent optimal debulking surgery that included radical hysterectomy, bilateral salpingo-oophorectomy, peritoneal stripping, and low anterior resection, as well as omentectomy in January 2016. The majority of the disease was primarily confined to the pelvis but with some nodules outside the pelvis. The frozen section during the surgery reported borderline tumor but with micro invasion. The final pathology was low-grade serous carcinoma arising in a typical serous borderline tumor. The left ovary also had a borderline tumor. The sigmoid colon, as well as the peritoneum from the urinary bladder, had invasive low-grade serous carcinoma present. Her final diagnosis was stage IIB, low-grade serous carcinoma. She was treated with six cycles of adjuvant chemotherapy with Carboplatin and Paclitaxel, completed in June 2016. She had a recurrence of the disease in 2017 with metastasis to the groin. She was treated with second-line chemotherapy with Carboplatin/Caelyx for six courses six cycles, then switched to a single-agent Caelyx and received four cycles with complete response. She had a second recurrence of the disease in 2018 and received third-line chemotherapy with Topotecan for a few cycles with disease progression and switched to Bevacizumab three weekly but deceased in August 2018 after two courses of treatment.

Patient 4

This 28-year-old nulliparous woman with a BMI of 21.5 had a laparoscopic assessment for an ovarian cyst in September 2009. Only peritoneal biopsies were taken, and final pathology reported borderline serous tumor. She underwent laparoscopic radical oophorectomy and staging in November of 2009. The final diagnosis was stage IIIC Micro papillary ovarian carcinoma with invasive implants. This patient received six cycles of adjuvant Carboplatin and

In July 2011, she had diagnostic laparoscopy and peritoneal biopsies, and a persistent disease was noted. She underwent secondary debulking, including bowel resection, in September 2011. She was treated with second-line chemotherapy with Carboplatin and Caelyx with minimal response.

After a second opinion, she was started on single-agent Topotecan and completed three cycles in May 2012 was discontinued due to intolerance. She was offered gemcitabine in April 2013 but declined due to possible side effects and a low response rate. She was started on three weekly bevacizumab and received 14 cycles with minimal side effects but stopped due to disease progression.

She was offered Tamoxifen 20 mg p.o bid and stopped due to intolerable side effects. At the beginning of 2017, the patient had a massive pulmonary embolism; imaging showed slow progression involving chest lymph nodes and increased collections in the abdominal cavity. The patient was deceased in August of 2017.

Patient 5

This patient was 47 years old woman, G0P0, BMI 25.1, presented with constipation and abdominal pain. She underwent primary surgery, including Laparotomy, en bloc resection of the sigmoid colon and rectum, total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral ureterolysis, in June 2018. The pathology was low-grade serous carcinoma, which was invading the bowel muscularis as well. The final diagnosis was Stage IIIC low-grade serous carcinoma. She received adjuvant chemotherapy with Carboplatin, Paclitaxel, and bevacizumab for four courses and only one cycle of bevacizumab due to poor wound healing. She underwent secondary debulking surgery with total colectomy and ileostomy and resection of a segment of the stomach in November 2018. After that, chemotherapy with CarboPaclitaxel resumed in January 2019, and bevacizumab was added in February 2019. After three courses of combination chemotherapy, she was having severe fatigue and did not want to continue bevacizumab maintenance. She was started on Letrozole 2.5 mg in June of 2019 and remains disease-free.

Results

The median age of patients was 46.4 (range, 28 to 60 years), and the median BMI was 25.12 (range, 20.35 to 30). 3 (60%) of patients underwent primary surgery, with the optimal tumor reduction achieved in all three patients. Four (80%) of patients received chemotherapy as a part of their initial treatment, and two (40%) of them had both neoadjuvant and adjuvant chemotherapy. Two (40%) of patients, in addition to chemotherapy, also received endocrine therapy. However, after their primary treatment, 3 (60%) patients were noted to have persistent or progressive disease. One (20%) patient died within three months after surgery. The median follow-up was 27 months (rate 3 to 80 months). Demographic data are shown in Table 1.

The clinicopathologic features of the ovarian tumors are summarized in Table 2. There were four low-grade serous ovarian carcinoma cases with invasive components and one case of a bilateral borderline serous ovarian tumor with a micro-invasive component.

The mean and median sizes of ovarian tumors were 7.24 cm and 7 cm, respectively (range 4.5 – 11.7 cm). The ovarian tumors were bilateral in all five cases. The micropapillary component was present in all five bilateral tumors.

Extraovarian disease with invasive implants was in all five cases, lymph node metastasis, foci of invasive carcinoma in the small bowel, colon, and omentum in one case; foci of invasive carcinoma in the peritoneum and colon in two cases, foci of invasive carcinoma in the bowel, fallopian tubes, and ovaries in one case, and foci of borderline serous ovarian tumor in the right and left pelvis, bladder, peritoneum and sigmoid colon in one case.

Molecular genetics analysis

Molecular analysis was performed in four cases (Table 3). In one case, an invasive micropapillary component contained BRAF mutation and did not have NRAS mutation. In one of these cases (case 3), the NRAS mutation was found in the micropapillary components of specimen 1 – right ovary, while BRAF mutation was not found. In the last case (case 4), neither BRAF nor NRAS has been found.

Age (years), mean (SD)	46.4 (13.7)
BMI (kg/m^2), median [IQR]	25.12 (3.73)
Race	**White**
Menopausal status:	
not in menopause	**3 (60)**
menopause	**2 (40)**
Pernicious habits:	
smoker	**1 (20)**
non-smoker	**4 (80)**
Initial Treatment, n (%)	
Surgery	**5 (100)**
Chemotherapy	
Neoadjuvant	**2 (40)**
Adjuvant	**5 (100)**
Endocrine therapy	**2 (40)**
Recurrence	**4 (80)**

Table 1: Patients Characteristics (n=5).

N	Patient's Age	Ovarian tumor size (cm)	Laterality	Tumor stage	Extraovarian disease
1	39	9.3	Bilateral	IIIC	Invasive implants in lymph nodes, small bowel, colon, omentum
2	59	8	Bilateral	IIIC	Invasive implants in ovary, sigmoid colon, omentum.
3	59	13; 9.5	Bilateral	IIB	Invasive implants SE, UBP, BWP
4	28	5; 12	Bilateral	I	Microinvasive implants of BSOT in the right and left pelvis, bladder, peritoneum, sigmoid colon
5	47	4.5	Bilateral	IIIC	Invasive implants in the small bowel, fallopian tuber, ovaries, and involving sigmoid colon

Table 2: Clinicopathologic features of the serous ovarian tumors with the invasive pattern.

Patient number	Tumor components analyzed	Mutational analysis		
		BRAF	NRAS	KRAS
1	Invasive MPSC	-	-	Negative
2	Invasive MPST	Positive	Negative	-
3	Non-invasive MPSC	-	Positive on specimen 1 – right ovary, and all negative on specimen 3 – abdominal wall	Negative
4	Invasive MPST	Negative	Negative	Negative

Table 3: Molecular analysis of the invasive components of the ovarian tumors.
*Case numbers correspond to the case list in table 2.
MPSC – Micropapillary serous carcinoma; MPST – Micropapillary (borderline) serous tumor

Discussion

Low-grade serous ovarian cancer is one of the rarest subtypes of ovarian cancer; moreover, there is currently not enough data on the prognosis of this disease and the treatment methods [7]. In this case series, we used five cases of low-grade serous ovarian carcinoma to review histology, assess the volume of low-grade serous ovarian carcinoma and the invasive implants, and correlate these findings with clinical presentation, outcome, and management.

In recent years, many genetic and molecular studies have been provided, based on which we can currently assume that low-grade serous ovarian carcinoma may occur following an initial diagnosis of a borderline serous tumor. Furthermore, in comparison with high-grade serous ovarian carcinoma (HGSOC), LGSOC has a lower mutation rate of p53 mutations, overexpression of estrogen receptors (ER), greater expression of progesterone receptors (PR), and as well as borderline serous tumors, mutations in KRAS and BRAF [8].

The primary treatment for low-grade serous ovarian carcinoma is surgery. For patients with an early stage of low-grade serous ovarian carcinoma is the main treatment and helps to determine the staging. In contrast, for patients with an advanced stage of LGSOC, cytoreductive surgery is performed, followed by platinum-based chemotherapy and endocrine therapy [8, 9].

However, low-grade serous ovarian carcinoma is known to be chemo-resistant and has poor outcomes. Even though low-grade serous ovarian carcinoma has a relatively good prognosis, about 80% of patients will have disease recurrence. Selected patients may be considered for the second cytoreductive surgery, especially if they are sensitive to platinum treatment and limited metastatic sites. Thus, most LGSOCs are estrogen receptor-positive, so endocrine therapy is a treatment option for patients with recurrent disease [9].

According to Gadduci et al., observation alone after staging surgery should be used for those with stage IA-IB disease, while chemotherapy or endocrine therapy may be utilized for those with stage IC-IIA disease. However, when the disease has progressed to stage IIb or IV, patients generally receive either chemotherapy (Carboplatin and Paclitaxel) for six cycles, followed by endocrine therapy, typically consisting of aromatase inhibitors, or continue with endocrine therapy alone [5].

For several years there are other treatments offered for LGSOC, such as endocrine therapy, molecularly targeted agents, and anti-angiogenesis inhibitors. However, the clinical diagnosis must be accurate in terms immunohistochemistry so that subsequent of histopathology and treatment will be determined correctly [16]. Tholander et al. reported that a patient with advanced LGSOC who received established treatment (combination treatment with dabrafenib and trametinib) had a complete response with combined BRAF and MEK inhibition [17]. However, at the moment, molecularly targeted agents, especially MEK inhibitors and CDK inhibitors, are being evaluated.

In our study, three patients had advanced–stage IIIC, one had stage IIB of low-grade serous ovarian carcinoma, and one had a borderline serous ovarian tumor. Patient 2 and Patient 5 with stage IIIC and Patient 3 with stage IIB underwent surgery as the first treatment step. After that, Patient 3 and Patient 5 had adjuvant chemotherapy (Carboplatin/Caelyx and Carboplatin, Paclitaxel, Avastin, respectively); however, Patient 2 faced postoperative issues and was deceased three months after surgery. Patient 1 and Patient 4 had neoadjuvant had neoadjuvant chemotherapy (a combination of carboplatin and Paclitaxel) as the first step of treatment 3 and 6 cycles. After that, both had surgery and adjuvant chemotherapy (Carboplatin. Paclitaxel, Avastin, and Carboplatin/Caelyx, accordingly). Unfortunately, all patients had a recurrence of the disease, secondary cytoreductive surgery, and chemotherapy; additionally, Patient 4 and Patient 5 received endocrine therapy (Tamoxifen and Letrozole, respectively). Currently, Patient 5 is alive, and she is receiving Letrozole as a monotherapy; other patients have died after disease progression within a year or less.

Tumors in this study demonstrated some morphological findings, including the presence of microscopic invasion, invasive carcinoma, and extra ovarian metastases. Four cases had a micropapillary serous invasive carcinoma, which is typical for low-grade serous carcinoma. In contrast, the macropapillary invasive component is less common and associated with its putative precursor of an atypical proliferative (borderline) serous tumor and non-invasive micropapillary serous carcinoma [6]. According to the histology reports, three cases (case 1, case 2, and case 3) had a background of borderline serous ovarian tumor, and in these cases, the micropapillary invasion was determined. We can conclude that the frequent association of micropapillary carcinomas with borderline serous tumors suggests that MPSC arises from BSOT; in other words, borderline serous tumor progresses to micropapillary serous carcinoma [10,11]. Case 4 was presented with borderline serous ovarian carcinoma with micropapillary invasive implants. According to Minagawa et al., borderline serous tumor with invasive implants simulates low-grade serous carcinoma and has a worse prognosis than tumors with non-invasive implants [12]. There is a consent that invasive peritoneal implants associated with borderline serous tumors have a poor prognosis of 7-year survival, which is about 66%, compared to non-invasive implants, where the survival rate was about 95.3% [11,12].

According to different studies, activating mutations have been reported in a borderline serous ovarian tumor (BSOT) and low-grade serous ovarian carcinoma (LGSOC), including KRAS, BRAF, and NRAS, which are members of the Ras sarcoma–mitogen-activated protein kinase (RAS-MAPK) pathway. KRAS and BRAF mutations are more common in SBOT and the early stages of LGSOC; moreover, additional driving events such as NRAS mutation occurs to facilitate the progression [13,14]. The BRAF mutation occurs to play protective role against the progression of a borderline serous ovarian tumor to low-grade serous ovarian carcinoma. Furthermore, it is the opposite of KRAS mutation, commonly occurring in SBOTs that recurred as LGSOCa. Moreover, SBOTs with KRAS mutation appears to represent a more aggressive phenotype [15].

In our study, KRAS mutation was not performed; BRAF and NRAS mutations were performed in case 2, case 3, and case 4. Case 2 and case 3 had a borderline serous tumor as a background of low-grade serous carcinoma; case 4 was presented with borderline serous carcinoma with a micropapillary invasive component. As a result, BRAF mutation was identified in one (case 2) of three cases, as well as NRAS mutation was detected in only one case (case 3).

Progression-free survival and overall survival rate cannot be estimated due to the small cohort of patients, the difference in treatment (2 patients had neoadjuvant chemotherapy), and the presence of another active cancer except ovarian in one of the patients.

In summary, low-grade serous ovarian carcinoma is known to be chemo resistant. Thus, surgical treatment is the first-line therapy for LGSOC and for the recurrence of the disease, followed by platinum-based adjuvant chemotherapy depending upon the stage and residual disease. Hormone therapy (e.g., aromatase inhibitors) is usually considered as a maintenance treatment after completing first-line treatment in all stages except stages 1A and 1B, where surgery is the only recommended treatment. Hormonal therapy can be offered as adjuvant and maintenance therapy after surgery in stage 1C without chemotherapy.

In the case of disease recurrence, the treatment strategy is similar; however, in recurrence cases, treatment is individualized and can be discussed with the patient, and the option to participate in a clinical trial is also considered. Moreover, knowing the mutation status of KRAS, BRAF, and NRAS, targeted therapy could be considered.

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

AA and RC conceived of the presented idea. AA focused on the clinical part. RC and ST performed the pathology part. AA encouraged MK to investigate literature on low-grade serous adenocarcinomas and supervised the findings of this work. AA, RC, ST, and MK were responsible for editing the manuscript. All authors discussed the results and contributed to the final manuscript.

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