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A Rare Case of Ovarian Serous Borderline Tumor Recurrence with Muscle Metastasis

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Data Interpretation D
Manuscript Preparation E
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Patient: Female, 50-year-old
Final Diagnosis: Ovarian cancer
Symptoms: Asymptomatic • elevated tumor biomarkers
Clinical Procedure: —
Specialty: Obstetrics and Gynecology • Oncology

Objective: Unusual clinical course

Background: Ovarian serous borderline tumors (SBTs) generally have a favorable prognosis, with a very low recurrence rate. However, in rare cases, they can recur as invasive low-grade serous carcinoma (LGSC) after a prolonged follow-up period. Here, we report a case of LGSC originating from SBT that recurred 23 years after the initial surgery, with metastasis to the quadratus lumborum muscle – an exceptionally rare site of metastasis.

Case Report: A 50-year-old woman, initially diagnosed with stage IIIC SBT and treated with complete tumor resection 23 years prior, presented with an asymptomatic recurrence detected by an elevated serum cancer antigen 125 (CA125) level. Contrast-enhanced computed tomography (CT) revealed multiple nodules suspected of peritoneal dissemination and a tumor infiltrating the quadratus lumborum muscle, suggesting recurrent SBT. A CT-guided needle biopsy confirmed that the tumor within the quadratus lumborum was a recurrence of SBT. Complete cytoreductive surgery was performed with the assistance of an orthopedic surgeon. Histopathological examination revealed progression to LGSC with cytoplasmic expression of the BRAF proto-oncogene (BRAF) V600E, indicating the presence of the *BRAF V600E* mutation, which is a characteristic feature of both SBT and LGSC. A retrospective review of CT images taken 10 years prior to the recurrence diagnosis showed a peritoneal tumor with calcification attached to the ileocecum, suggesting that the patient had remained asymptomatic for more than a decade after the actual onset of recurrence.

Conclusions: This case illustrates a rare instance of recurrent SBT with metastasis to the quadratus lumborum muscle. Given the exceptionally slow progression of recurrent SBT, long-term follow-up with CT imaging and serum CA125 monitoring is crucial for timely intervention and appropriate management upon recurrence.

Keywords: Ovarian Neoplasms • SBT • LGSC • Recurrence • Muscle Metastasis

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Introduction

Borderline ovarian tumors (BOTs) are characterized by histological features intermediate between benign cystadenomas and carcinomas. Due to their low malignant potential, recurrence may occur over an extended disease course, but it rarely leads to death. The reported 5-year and 10-year survival rates for BOTs, including all stages, are 95% and 90%, respectively. Even for stage IV cases, a 10-year survival rate of 77% has been documented [1,2].

Serous borderline tumor (SBT) is the most common type of BOT and accounts for 50% of all BOTs [3]. According to the 2020 WHO classification, SBT has 2 morphologic subtypes. Conventional SBT shows hierarchically branching papillae lined by stratified, heterogenous epithelium with up to moderate atypia, whereas micropapillary SBT shows multiple nonbranching filiform structures without fibrovascular cores that are 5 times longer than they are wide, originating directly from bulbous central stalks. Compared to conventional SBT, SBT with micropapillary pattern is reported to be associated with a higher recurrence rate and accounts for about 10% of all SBT [4]. Moreover, SBT is known to be a precursor lesion to low-grade serous carcinoma (LGSC), with sequence mutations in Kirsten rat sarcoma viral oncogene *(KRAS)* and BRAF proto-oncogene (*BRAF)* and very low numbers of deoxyribonucleic acid (DNA) copy number alterations. It has been reported that 6.8% of SBT results in recurrence with the development to LGSC, leading to disease progression and decreased overall survival [5,6]. *KRAS* mutation in SBT correlates with tumor recurrence rate and the development to LGSC in recurrent diseases [7,8], whereas *BRAF* mutations are less frequent in SBT with recurrence or progression to LGSC [9].

In this report, we present a case of conventional SBT with noninvasive peritoneal implants that, after 23 years of follow-up, recurred with multiple peritoneal dissemination and a solitary quadratus lumborum muscle metastasis in the form of LGSC. Muscular metastasis is very rare in recurrence for SBT and LGSC because the site of recurrence for SBT and LGSC is primarily intraperitoneal and retroperitoneal lymphatic [10]. There are multiple reports on the metastatic sites for SBT and LGSC, whereas there is just a single report of SBT with muscle metastasis. We did complete cytoreductive surgery with the cooperation of orthopedic surgeons, because SBT and LGSC are poorly sensitive to chemotherapy (carboplatin and paclitaxel) unlike high-grade serous carcinoma, and complete second cytoreductive surgery at recurrence is associated with improved progression-free survival and overall survival [11,12]. Retrospectively, a calcified tumor adhering to the ileocecum in computed tomography (CT) images and an elevated serum cancer antigen 125 (CA125) level was observed 10 years prior to the diagnosis of recurrence. This case provides a unique insight into the natural progression of recurrent SBT.

Case Report

This 50-year-old nulliparous woman with abdominal distention was diagnosed with SBT at International Federation of Gynecology and Obstetrics (FIGO) stage IIIC and underwent complete cytoreductive surgery 23 years ago, when she was 27 years old. She had no particular medical, family, or psychosocial history. The complete cytoreductive surgery included total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, partial omentectomy, and sigmoid and rectal resection. The postoperative pathological diagnosis was conventional SBT, which did not show a micropapillary pattern, and non-invasive peritoneal implants and pelvic lymph node metastases were observed. At this stage, due to the absence of significant nuclear atypia and invasive features, the diagnosis was established as SBT rather than LGSC (**Figure 1A**). Postoperative adjuvant chemotherapy with 3 courses of paclitaxel and carboplatin was administered. The serum level of CA125, which had been elevated preoperatively at 74 U/mL, had normalized and no recurrence was observed over a long period. The patient visited the hospital regularly for follow-up and estrogen replacement therapy because she had had both ovaries removed. During the follow-up period, serum CA125 level was measured, and CT scans were performed once a year for up to 15 years after the initial treatment, and serum CA125 level was measured once every few years after 15 years. Serum CA125 levels began to exceed 10 U/mL 16 years after the initial treatment. After that, the CA125 level gradually increased, albeit very slowly.

Twenty-three years after surgery, her serum CA125 level exceeded 35 U/mL (**Figure 2**). Although she had no symptoms at all, we performed a detailed examination with contrast-enhanced CT, which revealed numerous nodules suspected of peritoneal dissemination and a tumor infiltrating the quadratus lumborum muscle, suggesting recurrence of SBT (**Figure 3**). Positron emission tomography (PET)-CT also showed accumulation of ^{18}F-fluorodeoxyglucose (FDG) at the sites of suspected recurrence and did not detect another metastasis (**Figure 3**). Peritoneal dissemination is a common site of recurrence in SBT, but metastasis to the quadratus lumborum muscle is extremely rare, so we decided to histologically confirm whether it was indeed the recurrence. A CT-guided needle biopsy of the quadratus lumborum muscle tumor and peritoneal dissemination led to a diagnosis of recurrent SBT.

We scheduled a secondary debulking surgery, because SBT and LGSC are poorly sensitive to chemotherapy (carboplatin and paclitaxel) and complete second cytoreductive surgery at recurrence are associated with improved progression-free survival and overall survival. Due to the extensive spread of the lesion and the operative positions, we determined that a one-stage surgery would be difficult. Since there was a high risk of

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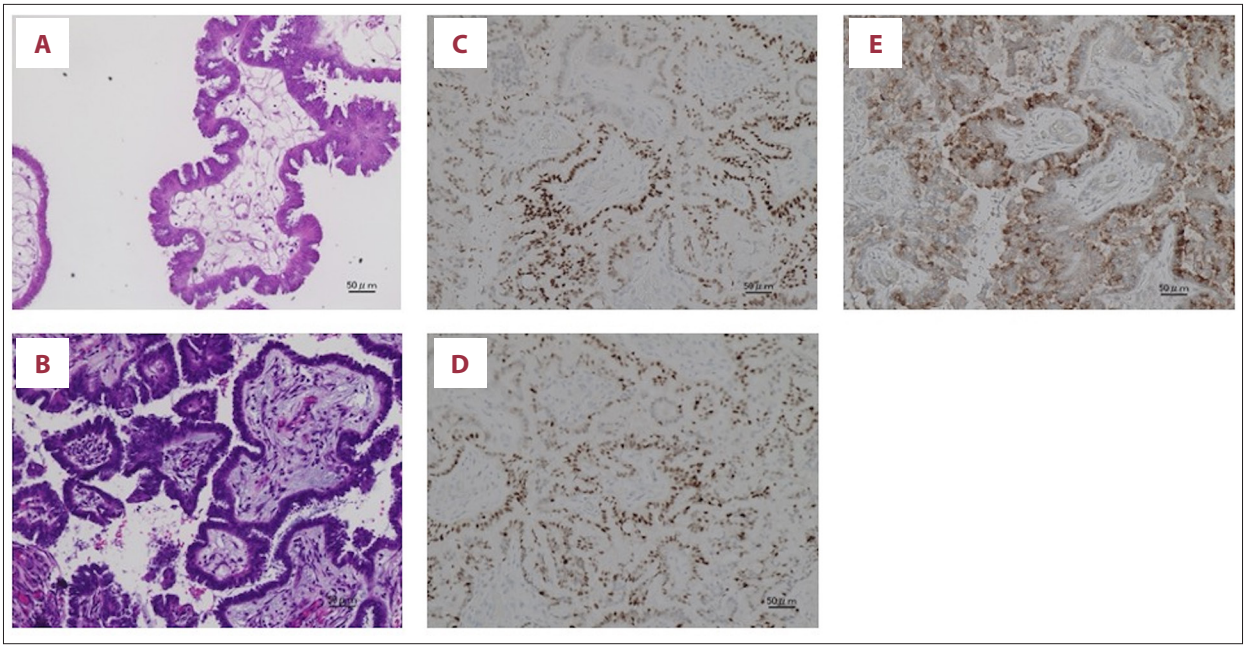

Figure 1. Pathology images of the primary and recurrent tumors at high-power field (200×). (**A**) Hematoxylin-Eosin (HE) staining of the primary tumor, (**B-E**) the recurrent peritoneal dissemination; (**B**) HE staining, (**C**) estrogen receptors, (**D**) progesterone receptors and (**E**) BRAF V600E cytoplasmic staining. Scale bars: (**A-E**) 50 µm.

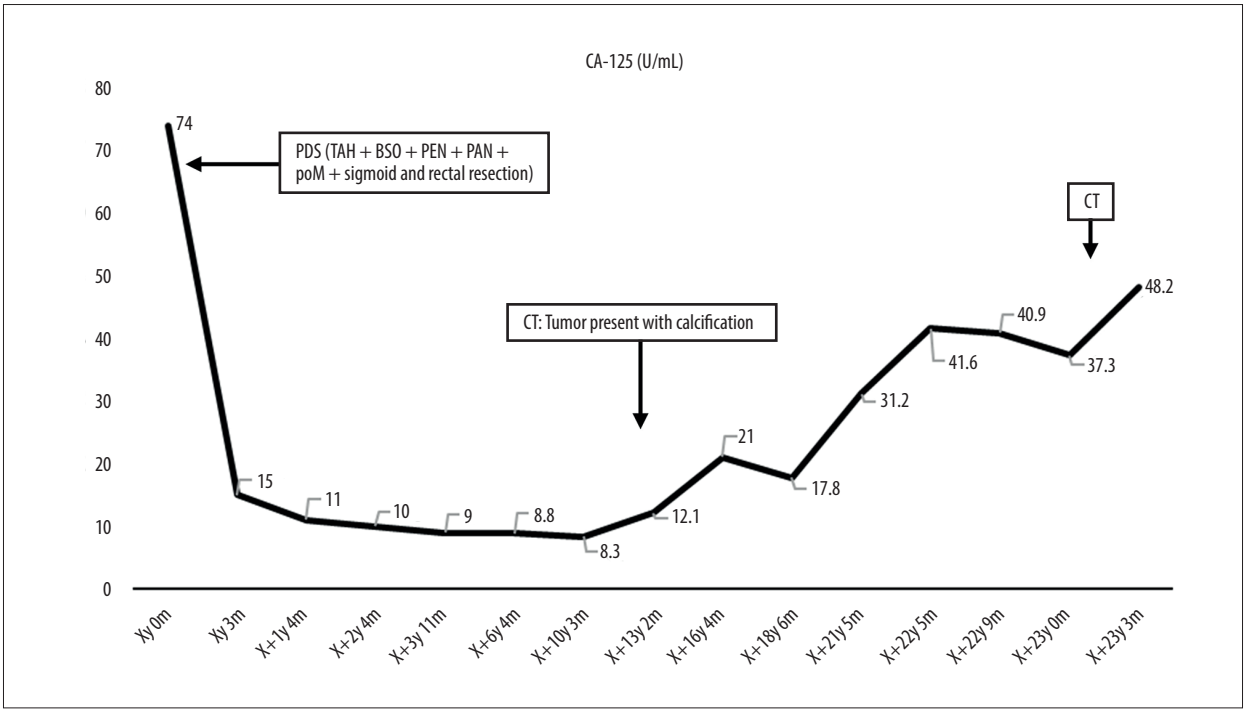

Figure 2. Serum level of CA-125 from 23 years before to diagnosis of recurrence. PDS – primary debulking surgery; TAH – total abdominal hysterectomy; BSO – bilateral salpingo-oophorectomy; PEN – pelvic lymphadenectomy; PAN – para-aortic lymphadenectomy; pOM – partial omentectomy; CT – computed tomography; y – years; m – months.

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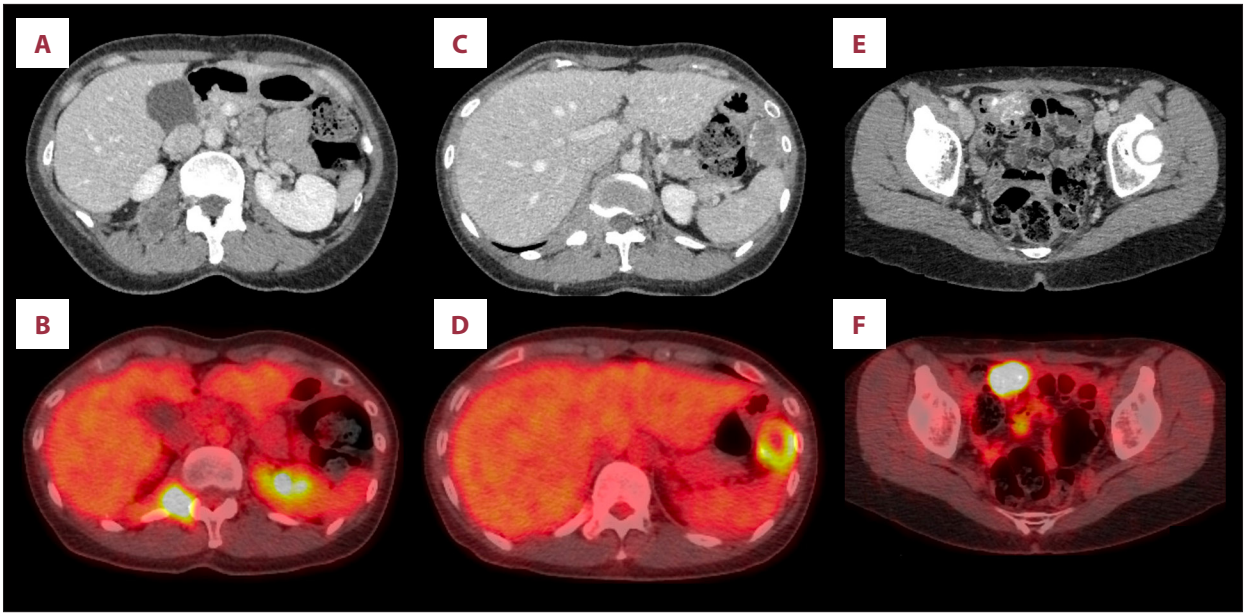

Figure 3. Findings on CT and PET-CT on the recurrent tumors. (**A, B**) images of right quadratus lumborum muscle metastasis, (**C, D**) images of the recurrent tumor on the greater curvature of stomach and (**E, F**) images of tumor near the ileocecal region. (**A, C, E**) contrast-enhanced CT images and (**B, D, F**) PET-CT images.

infection in abdominal surgery, and even though there were no symptoms, there was a possibility that spinal symptoms would appear in the future if the tumor grew and invaded the spine. Orthopedic surgeons first performed tumor resection in the quadratus lumborum and psoas major muscles via a retroperitoneal approach, followed by intra-spinal canal tumor curettage with posterior spinal fusion at the T12-L1 segment (**Figures 4A, 5A**). The tumor had not extended intraperitoneally. The operation time was 7 hours 50 minutes, and the blood loss was 180 mL. The surgery was completed without complications, and complete resection of the invasive tumor within the quadratus lumborum muscle was achieved. In the resected specimen, edematous or gelatinous white papillary structures were observed against a background of muscle tissue. Microscopically, a papillary structure lined by low-grade atypical epithelium was identified, with irregular glandular ducts and individual cells proliferating within a fibrous stroma. While the histological features were consistent with a recurrence of SBT, the diagnosis was determined to be LGSC due to the invasive growth within the muscle tissue.

One month after orthopedic surgery, we performed a resection of the peritoneal dissemination. Intra-abdominal findings showed numerous small disseminations on the diaphragm and 2 on the surface of the liver. We found a 3-cm tumor on the lesser curvature of the stomach, a 5-cm tumor on the greater curvature, a 7-cm tumor in the left paracolic gutter (**Figures 4B-4D, 5B-5D**). The tumor on the greater curvature had infiltrated the gastric wall. Other disseminations were also observed on the cecum and ileum, as well as in the mesentery of the small intestine. A small amount of bloody ascites was observed. Surgery included diaphragm stripping, hepatic surface tumor resection, resection of perigastric tumors with partial gastrectomy, combined resection of the cecum and small intestine, preserving the ileocecal region, and pelvic peritoneal stripping. We achieved complete cytoreductive surgery. An ostomy was not created; instead, the transected segments of the small intestine were anastomosed. The duration of the surgery was 11 hours 10 minutes, with a recorded blood loss of 2050 mL. The cytological examination of the ascites was positive for adenocarcinoma. In the microscopic examination of the resected specimen, the areas suspected of peritoneal dissemination on the liver surface were found to be inflammatory changes. However, in other areas, proliferation in papillary, cribriform, and glandular patterns with associated calcification was observed, consistent with the findings of LGSC. Immunohistochemical staining results indicated positive staining for estrogen receptors, progesterone receptors, and BRAF V600E (**Figure 1B-1E**). The BRAF V600E cytoplasmic pattern indicates the presence of the *BRAF V600E* mutation, which is commonly observed in SBT and LGSC. Her postoperative course was favorable. In a retrospective review, a CT image taken 10 years before the diagnosis of recurrence showed a 2-cm nodular lesion with calcification attached to the ileocecum (**Figure 6**). During this period, CA125 levels remained within the normal range, but there was a slight upward trend. From these findings, it was determined that signs of recurrence had been present for at least 10 years.

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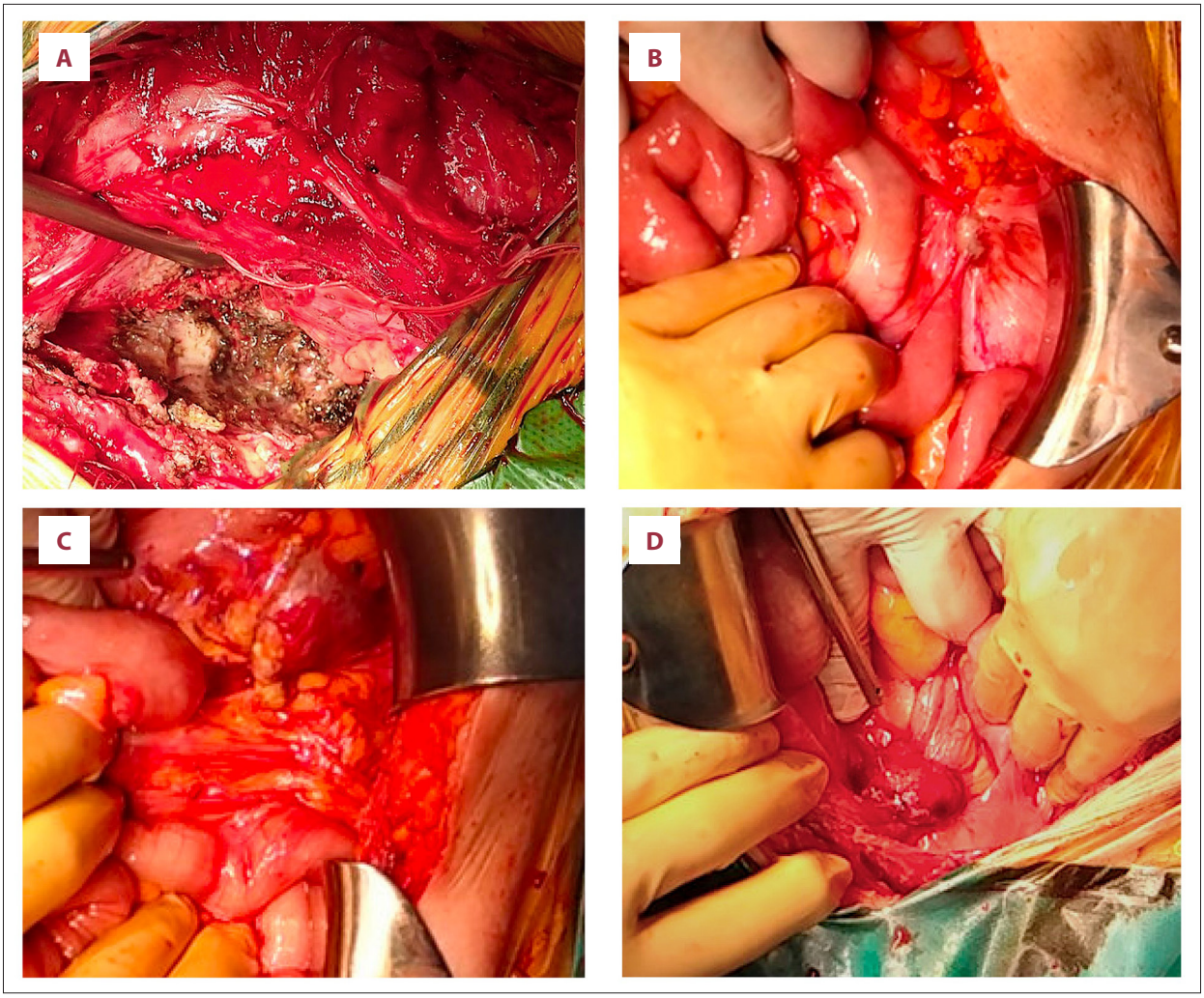

Figure 4. Intraoperative images of second cytoreductive surgery. (**A**) the resection of a quadratus lumborum muscle metastasis, (**B**) the tumor on the greater curvature of stomach, resected en bloc with a portion of the gastric wall, (**C**) the tumor on the left paracolic gutter (**D**) the tumor attached to the ileocecum.

We proposed postoperative adjuvant chemotherapy with carboplatin, paclitaxel, and bevacizumab 6 weeks after the second surgery, but the patient opted against it. Consequently, no adjuvant therapy was administered, and the patient remained under close observation.

Discussion

We managed a case of ovarian LGSC originating from SBT that recurred 23 years after initial treatment. Metastasis was observed within the peritoneal cavity and in the quadratus lumborum muscle, which is an extremely rare site of recurrence. SBT usually spreads transperineally, and sometimes has lymphogenous metastasis. The mechanism of metastasis to muscles has not been fully elucidated, but hematogenous metastasis is thought to be the most likely route because the tumor in our patient had not extended intraperitoneally. The literature contains only 1 case report of LGSC with paraspinal metastasis on the right arch of the 12th thoracic vertebra, which showed right-lateral chest pain and neurologic abnormalities in the lower limbs [13], without peritoneal metastasis. Some other reports showed breast or brain metastasis, which are also thought to be a hematogenous route [14,15], indicating that SBT/LGSC can very rarely metastasize in a way that differs from peritoneal dissemination or lymph node metastasis.

We completed cytoreductive surgery with the help of an orthopedic surgeon because LGSC is less responsive to conventional chemotherapy. If complete cytoreductive surgery is not possible, systemic therapy must be chosen. In 2022, the US Food and Drug Administration (FDA) approved the combination of dabrafenib (a BRAF inhibitor) and trametinib (a mitogen-activated protein kinase (MEK) inhibitor) for unresectable or metastatic

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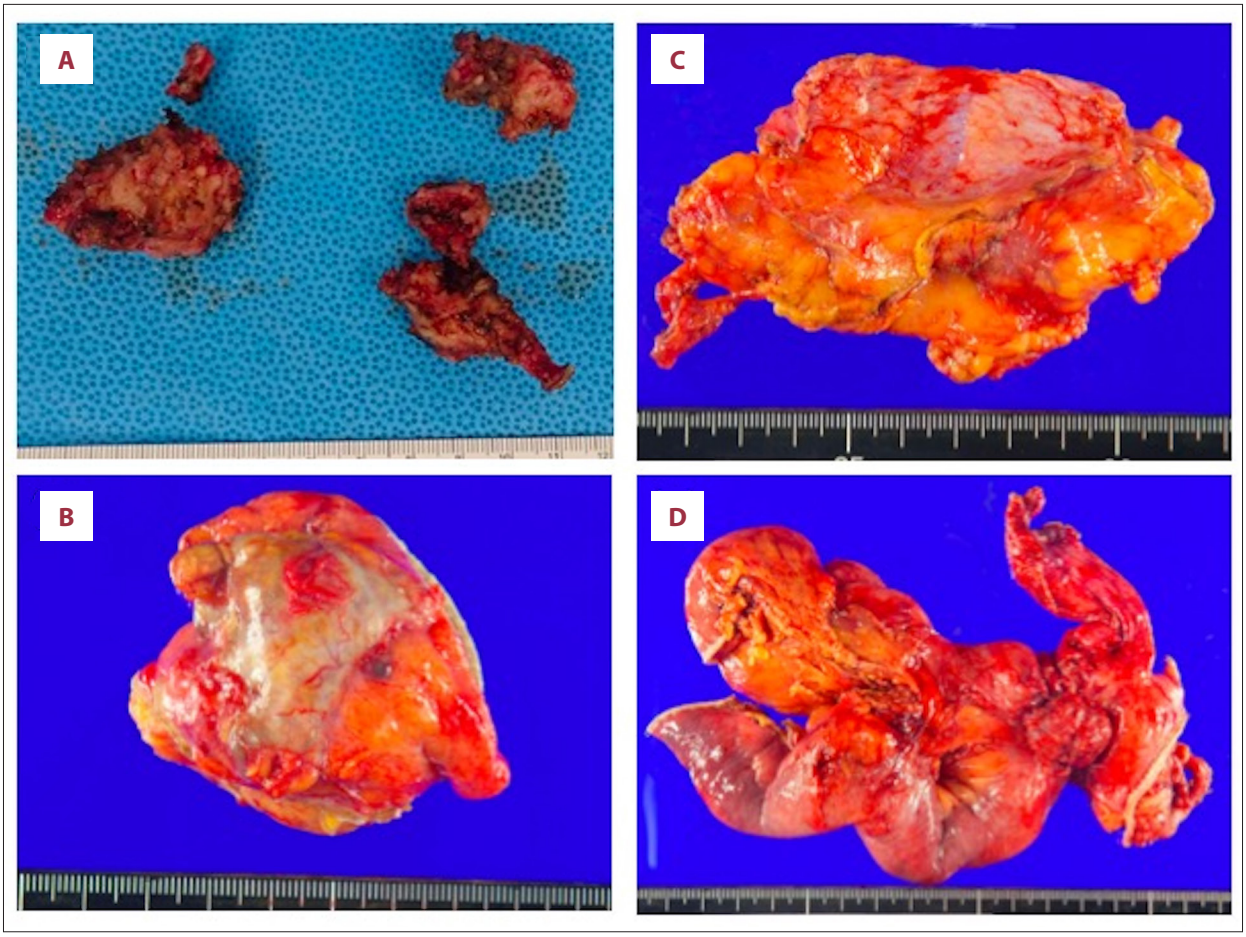

Figure 5. Specimen images. (**A**) The right quadratus lumborum muscle metastasis, (**B**) the tumor on the greater curvature of stomach, (**C**) the tumor in the left paracolic gutter and (**D**) the tumor attached to the ileocecum resected with the partial ileum and cecum.

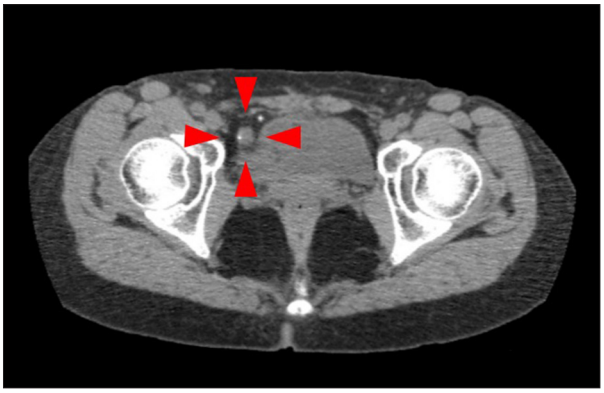

Figure 6. A calcified tumor visible on CT images performed 10 years prior to the diagnosis of recurrence (arrowheads).

solid tumors with *BRAF V600E* mutation. Mutations involving *BRAF V600E* have been identified in 35% of SBT and LGSC [16]. A recent clinical trial (GOG281/LOGS) demonstrated the efficacy of trametinib in treating recurrent LGSC [17]. The sustained efficacy of dabrafenib monotherapy for recurrent LGSC has also been reported [18], but as it was a single case report, further verification is needed. For other options, data from the MITO22 study suggest the efficacy of bevacizumab. The addition of bevacizumab to chemotherapy for advanced or recurrent LGSC has been reported to improve PFS [19]. Since many LGSCs demonstrate expression of the ER, as in our case, anti-estrogen therapies such as aromatase inhibitors and tamoxifen were tested in clinical trials. However, the GOG281 study showed that letrozole, an aromatase inhibitor, and tamoxifen were less effective than trametinib in treating recurrent LGSC, suggesting that anti-estrogen therapies might not be effective at recurrence. Another approach that is currently being considered is adjuvant endocrine therapy. There are several clinical trials underway that use aromatase inhibitors as an adjuvant endocrine therapy [20,21]. Carboplatin-based chemotherapy in combination with pembrolizumab (PERCEPTION, a phase II study) is also being tested. The results of these clinical trials are eagerly awaited.

The need for adjuvant chemotherapy following cytoreductive surgery for recurrent LGSC has been controversial. We predicted

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Table 1. Report of the recurrence rate and time to recurrence of SBT.

Author	Stage (n)	Recurrence rate	Time to recurrence	Follow-up period (year)
Silva et al, (2006) [23]	Stage II: 29 Stage III: 50 Stage IV: 1	44% (35/80)	<5 y: 10% (8/80) 5 to 10 y: 18.8% (15/80) 10 to 15 y: 10% (8/80) >15 y: 5% (4/80)	5 to 31 (median 15.7)
Baba et al, (2023) [12]	Stage I: 250 Stage II-IV: 39	4.2% (12/289)	10-year PFS: 92.3%	No data available
Song et al, (2012) [24]	Stage I: 71	9.9% (7/71)	0.8 to 6.2 y (median 3.2)	1 to 13 (median 4.7)
Gilks et al, (2003) [25]	Stage II: 15 Stage III: 34	28.6% (14/49)	1 to 8 y (mean 3.5)	3 to 18 (median 6)

that the addition of bevacizumab to carboplatin and paclitaxel would be effective based on the data from the MITO22 trial, and we proposed it to the patient. We did not propose the combination of dabrafenib and trametinib due to BRAF V600E expression of the recurrent tumor, since it was not approved for use in adjuvant therapy in our country. The 2019 edition of the European Society for Medical Oncology (ESMO) and European Society of Gynecological Oncology (ESGO) guidelines do not recommend the administration of adjuvant chemotherapy for SBT, as the benefits of such treatment have not been clearly established [22]. Although it has been reported that adjuvant chemotherapy after primary cytoreductive surgery does not improve overall survival in patients with advanced-stage LGSC, as mentioned above, clinical trials are being conducted as postoperative adjuvant therapy, and the results are awaited.

In this case, although the initial signs of recurrence were not recognized, long-term follow-up enabled the diagnosis of asymptomatic recurrence 23 years after surgery. This follow-up also served as part of estrogen replacement therapy (ERT). Hormone replacement therapy has been reported to increase the incidence of SBT [11]. Although the immunohistochemical staining of the recurrent tumor in this case was positive for ER, suggesting that ERT could potentially have an adverse effect on the recurrence of SBT, there are no reports that estrogen administration after SBT surgery is a risk factor for recurrence. Considering the course of our case, it can be inferred that ERT did not cause the rapid growth of the tumor, as the tumor continued to recur for 23 years despite the administration of ERT.

It should be noted that there is no clear consensus regarding the optimal follow-up period for SBT. We reviewed the recurrence rate and time to recurrence of SBT based on previous reports (**Table 1**) [22-25]. Advanced stages tend to be associated with a slightly higher recurrence rate, and a longer follow-up period may also be linked to a modest increase in the incidence of recurrence. Long-term follow-up is necessary because a short follow-up period may miss recurrence. In fact, 5% of SBT patients with stage II or higher have recurrence more than 15 years later [23]. It may be better not to terminate follow-up after 15 years. Previous reports suggest a correlation between proliferative activity and serum CA125 levels in SBT [26]. In cases of SBT with indolent progression and minimal increases in CA125 levels, it might be possible to detect recurrence through periodic CT examination conducted every few years, thereby facilitating timely therapeutic intervention. In routine gynecological ultrasound examinations, the observation is usually limited to the pelvic region, allowing for detection of abnormalities within the pelvis. However, in cases like ours, where metastasis to the quadratus lumborum muscle has occurred, a whole-body examination using CT or other imaging modalities is necessary.

Conclusions

We managed a rare case of SBT recurrence and metastasis to the quadratus lumborum. Recurrence usually occurs as peritoneal dissemination or lymph node metastasis, but it is necessary to be careful because in rare cases it can metastasize to such unusual sites.

In this case, we suspected recurrence based on the rise in serum CA125 level, and diagnosed recurrence using CT and CT-guided biopsy. Complete cytoreductive surgery is the first choice for treatment at the time of recurrence, but in cases where complete resection is difficult, a combination therapy with a BRAF inhibitor and a MEK inhibitor is also useful, as some SBTs and LGSCs have *BRAF V600E* mutation. In addition, new treatment options such as the addition of bevacizumab to paclitaxel and carboplatin are also being investigated.

Recurrent SBT progresses extremely slowly, and in some cases recurrence occurs more than 15 years after initial diagnosis, so it is important to carefully consider when to end follow-up observation.

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Patient consent

Informed consent or substitute for it was obtained from the patient.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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