CANCER DIAGNOSIS & PROGNOSIS
3: 360-364 (2023) doi: 10.21873/cdp.10224

Clinical Features of Borderline Ovarian Seromucinous Tumor

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Abstract. *Background/Aim: Ovarian seromucinous tumor is a histological type of ovarian neoplasm. Although seromucinous borderline tumors (BSMT) are associated with endometriosis, the frequency of their occurrence is low, and many aspects of their behavior remain unclear. In this study, we aimed to clarify the clinicopathological factors of BSMT. Patients and Methods: We retrospectively reviewed 32 patients with pathologically diagnosed BSMT who underwent surgery at Jikei University Hospital. The survey items were patient characteristics, such as age, initial symptoms, preoperative tumor markers, surgical procedure and stage of surgery, presence of endometriosis, and recurrence. Results: The median age was 45 years. Lower abdominal pain was the most common chief complaint, about one-third of patients were asymptomatic; one-sixth were discovered during follow-up for endometriosis. The majority had a high serum CA19-9 level. Twenty-five patients (78.1%) had unilateral masses, whereas seven patients (21.9%) had bilateral masses. More than 90% of the cases had coexisting endometriosis histologically. Thirty cases (93.8%) were stage I, only two were stage II, and none were stage III or IV. Recurrence was observed in two cases: one was borderline malignant and the other was a carcinoma. Conclusion: BSMT is a rare form of borderline malignancy. Its preoperative diagnosis is often difficult because of various clinical findings, but a history of endometriosis and an elevated serum CA19-9 level may aid in some cases.*

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Key Words: CA-19-9 antigen, cystadenofibroma, endometriosis, ovarian neoplasms, recurrence.

Borderline ovarian seromucinous tumor (BSMT) is a papillary neoplasm composed of an admixture of Müllerian type epithelia, lacking confluent or destructive invasion (1). Historically, it was known as endocervical-type borderline mucinous tumor, borderline Müllerian mucinous tumor, or mixed-epithelial borderline tumor of Müllerian type. In the World Health Organization (WHO) Classification of Gynecologic Tumors, BSMT was first introduced in the fourth edition published in 2014 (2). Its benign counterparts, namely seromucous cystadenoma and seromucinous cystadenofibroma, are rare, while its malignant counterpart is classified as a variant of endometrioid carcinoma in the fifth edition published in 2020 (1). BSMT is often associated with endometriosis (3, 4).

Although various clinical, pathological, and molecular features of BSMT were elucidated, studies focusing on its clinicopathological features with a large number of cases treated at a single institution are few because of its relatively rare occurrence. Herein, we retrospectively examined cases of BSMT treated at a single institution to explore its clinicopathological features.

Patients and Methods

This study was conducted with the approval of the Ethics Committee of the Jikei University School of Medicine [Approval No. 32-465(10557)].

Case selection. Surgical pathology archives of the Jikei University Hospital between January 2001 and December 2017 were searched for ovarian borderline tumors. All hematoxylin and eosin-stained slides were reviewed by two pathologists (TK and NF) to confirm the histological type of tumors based on WHO 2020 criteria (1).

Patients' background data, preoperative serum tumor marker levels and imaging findings, surgical procedure, status of intraoperative consultation, surgical stage according to the International Federation of Gynecology and Obstetrics staging system (2014) (5), and prognosis were obtained from medical records.

Pathological findings. Gross descriptions of tumors were obtained from pathology reports. The following histological findings were also examined: Presence of micropapillary pattern in BSMT; presence of endometriosis in the ipsilateral ovary, contralateral ovary, or pelvic peritoneum; presence of endometrial neoplasm in those with hysterectomy, lymph node status, and tumors at the time of recurrence.

Results

Thirty-two patients with ovarian BSMT were included. The patients' median age was 45 years (range=22-72 years), and 25 out of 32 patients (78%) were premenopausal (Table I). Lower abdominal pain was the most common symptom (13 patients, 40.6%), but about one-third of patients were asymptomatic (n=11, 34.4%) and were diagnosed during a medical check-up. In five patients (15.6%), malignant tumor was suspected based on ultrasound during follow-up for endometriosis. One patient presented with abnormal genital bleeding. In two patients, the chief complaint was unknown. Twenty-two patients (68.8%) had no history of pregnancy.

Preoperative serum carbohydrate antigen 19-9 (CA19-9) levels were elevated in 19 cases (59%), and serum CA125 was elevated in 15 (47%) cases. Twelve patients (37.5%) had elevated levels of both CA19-9 and CA125, whereas in 10 patients (31.3%), both tumor markers were within normal limits. Endometriosis was diagnosed in 25 cases (78.1%) based on preoperative transvaginal ultrasonography and imaging studies.

Operative details and results are shown in Table II. Of 32 patients, 12 (37.5%) underwent staging laparotomy (bilateral salpingo-oophorectomy, total abdominal hysterectomy, and omentectomy), followed by lymph node biopsy or dissection. Four patients underwent bilateral salpingo-oophorectomy, total abdominal hysterectomy, and omentectomy. Sixteen patients underwent tumorectomy or unilateral salpingo-oophorectomy to preserve their fertility. Intraoperative consultation was performed in 28 patients; 26 were diagnosed with borderline tumor, and two were borderline tumors or carcinoma. The tumors varied in size, ranging from 2.5 to 20 cm, with a median of 6.4 cm. Tumor was unilateral in most cases (78.1%). Histological examination confirmed coexistent endometriosis in 30 patients (93.7%); it was in the ipsilateral ovary in 24 (80%) and in the contralateral ovary and pelvic peritoneum in addition to the ipsilateral ovary in six (20%). Thirty cases were stage I, and only two cases were diagnosed as stage II.

Follow-up information was available for all 32 patients, with a range of 1-211 months (median=71 months). Only two (6.3%) had recurrences; one only underwent tumorectomy initially, and unilateral salpingo-oophorectomy and omentectomy were performed when BSMT recurred in the ipsilateral ovary 8 years later. In another patient, the initial surgery was staging laparotomy to prove stage IIB BSMT with noninvasive peritoneal implants and a concurrent endometrial endometrioid carcinoma grade 1 (pT1apN0). Her ovarian BSMT had both exophytic and intracystic growth, with the latter having a micropapillary component. She also had a mesenteric mass and enlarged para-aortic lymph nodes found intraoperatively; these were pathologically proven to be follicular lymphoma. Fifteen months after the initial surgery, another mesenteric tumor was found, and the resected tumor was grade 1 endometrioid carcinoma with an BSMT component. Paclitaxel/carboplatin chemotherapy regimen was unsuccessful, and the patient died 2 years and 7 months after the initial surgery.

Discussion

Although histological and genetic characteristics of BSMT have been reported, there are few characteristic biomarkers, and it is not easy to estimate BSMT clinically. Therefore, it is important for the surgeon to know the clinical characteristics such as fluctuating tumor markers and frequent complications of endometriosis, as well as the gross appearance of the explanted specimen. Regarding tumor markers, this study showed that the serum CA19-9 level is often elevated in patients with BSMT (59.4%); this finding was only given limited attention in previous reports. Indeed, in 19 out of 32 patients with elevated serum CA19-9 level in this study, in five it exceeded 1,000 U/ml, and the highest was 3,471 U/ml. CA19-9 is best known as a useful marker for mucinous tumors of the pancreas and biliary tract, with a relatively high sensitivity and specificity. It is localized in the pancreatic and biliary parenchyma (6). CA19-9 is also elevated in various diseases, including mucinous ovarian tumors, teratoma, endometriosis, benign hepatic and pulmonary diseases, thyroiditis, diabetes mellitus, and autoimmune diseases (6). Its elevation is explained by inflammation and proliferation of non-tumorous tissues or metabolic malfunction. BSMT is histologically characterized by neutrophilic infiltration into the stroma and epithelium, and these inflammatory findings in tumors may be associated with an elevated serum CA19-9 level. Regarding the relationship of serum CA19-9 to the histological subtypes of ovarian tumors, Nakagawa *et al*. reported that the serum CA19-9 levels in patients with borderline ovarian mucinous tumors and endometriotic cysts were significantly elevated compared with those in control individuals and that CA19-9 can be useful for preoperative evaluation (7). It is

Table I. *Characteristics of patients in this study (n=32 patients).*

Characteristics	N (%)
Age, years	
Median (range)	45 (22-72)
<40 Years	10 (31.2%)
≥40 Years	22 (68.8%)
Menopausal status	
Premenopausal	25 (78.1%)
Postmenopausal	7 (21.9%)
Chief complaint	
Abdominal pain	13 (40.6%)
No symptoms	11 (34.4%)
Endometriosis*	5 (15.6%)
Other	1 (3.1%)
Unknown	2 (6.3%)
Parity	
0	22 (68.8%)
≥1	10 (31.2%)
Preoperative serum tumor markers	
CA19-9	
≤37.0 U/ml	13 (40.6%)
>37.0 U/ml	19 (59.4%)
Median (range), U/ml	169 (42-3,471)
CA125	
≤35.0 U/ml	17 (53%)
>35.0 U/ml	15 (47%)
Median (range), U/ml	198 (38-10,035)
CA19-9/CA125	
Positive for both	12 (37.5%)
Negative for both	10 (31.3%)
Endometriosis*	
Yes	25 (78.1%)
No	4 (12.5%)
Unknown	3 (9.4%)
Recurrence	
Yes	2 (6.3%)
No	30 (93.7%)

*History, ultrasound/magnetic resonance imaging findings.

Table II. *Operative details and results.*

	N (%)
Surgical procedure, n (%)	
Staging laparotomy[a]	12 (37.5%)
Standard laparotomy[b]	4 (12.5%)
Fertility-sparing staging laparotomy[c]	16 (50%)
Intraoperative diagnosis, n (%)	
Benign	0
Borderline	26 (81.3%)
Carcinoma	0
Borderline/carcinoma	2 (6.2%)
Not made	4 (12.5%)
Tumor size, cm	
Median (range)	6.4 (2.8-20)
Site of tumor, n (%)	
Unilateral	25 (78.1%)
Bilateral	7 (21.9%)
Yes	30 (93.7%)
Endometriosis*, n (%)	
Ipsilateral	24 (80%)
Contralateral or pelvis	6 (20%)
No	2 (6.3%)
Stage, n (%)	
I	30 (93.8%)
IA	18 (56.3%)
IB	3 (9.4%)
IC[d]	9 (28.1%)
II	2 (6.2%)
III-IV	0

*Histologically confirmed in the surgical specimens. [a]Bilateral salpingo-oophorectomy with hysterectomy, omentectomy, lymph node biopsy or lymphadenectomy. [b]Bilateral salpingo-oophorectomy with hysterectomy, omentectomy. [c]Unilateral salphingo-oophorectomy and tumorectomy or bilateral tumorectomy with or without omentectomy. [d]Non-invasive implant present.

particularly interesting that serum CA19-9 levels were higher in those with endocervical type tumors, which corresponds to the current definition of BSMT, than in the intestinal type. BSMT is frequently associated with endometriosis, as shown in literature (3, 4, 8) and in the present study, and is usually accompanied by prominent neutrophil infiltration, thus it may be responsible for CA19-9 elevation. However, in some cases in this study, serum CA19-9 was not elevated despite the presence of endometriosis or neutrophil infiltration in tumors. The mechanism of this elevation requires further investigation.

BSMT is included in endometriosis-related ovarian neoplasms, along with clear-cell carcinoma and endometrioid carcinoma (8). In this study, 25 patients (78.1%), including five who had endometriotic cysts, had preoperative imaging studies indicating the presence of endometriosis. In 93% (30/32) of patients with surgically removed ovaries, a histological diagnosis of coexistent endometriosis was found; this was more frequent than what was previously reported. Of the 30 patients with endometriosis, six (20%) had endometriosis in the contralateral ovary or pelvic peritoneum. One possible reason for the higher frequency of coexisting endometriosis in this study is the number of tissue sections taken at our institution, which was at least one section per 1 cm of tumor diameter.

In this study, two patients (6.3%) had recurrence. While the recurrence rate of borderline ovarian tumors is 5-33% generally (9), Hada *et al*. reported a rate of 18% for BSMT, suggesting that the association with endometriosis may be a factor that increases recurrence (10). Ren *et al*. reported that conservative surgical procedures, cyst rupture, advanced International Federation of Obstetrics and Gynecology stage, microinvasion, and peritoneal implants are risk factors for

recurrence of BSMT (11). Another report showed a recurrence rate of 14-20.5% with conservative surgery compared to 0-7% with radical surgery (12). In fact, one of the patients with recurrence in the present study only underwent tumorectomy initially. It is noteworthy that one patient in our study whose initial surgery was staging laparotomy to prove stage IIB BSMT with non-invasive peritoneal implants and pT1apN0 developed peritoneal carcinoma at the time of recurrence. It is possible that the non-invasive peritoneal implant progressed to cancer; another possibility is that ovarian or peritoneal diseases had a carcinoma component, which was not pathologically detectable. Koskas *et al*. reported that three cases of endocervical-like borderline mucinous tumors and mixed-epithelial borderline tumors, which are currently called BSMT, recurred during a 10-year follow-up, with two recurring as invasive carcinomas (13). It is known that 2-3% of borderline ovarian tumors develop as invasive carcinoma at the time of recurrence (14, 15). In a review of 130 cases of borderline malignancies, including those who underwent conservative surgery, Oh *et al*. reported 11 (8.5%) recurrences; four cases recurred as borderline malignancies, while seven cases had a histological diagnosis of carcinoma (9). Based on these reports, it is more likely that the non-invasive peritoneal implant progressed to cancer in our patient. Although borderline ovarian tumors are generally considered to have a favorable prognosis and survival rates, which do not differ significantly among histological types (16), it should be noted that rare BSMTs of advanced stages may develop as cancer in the peritoneum and result in a poor prognosis. When only performing tumorectomy or unilateral salpingo-oophorectomy in a patient with BSMT for fertility sparing, it is essential to understand that BSMT is often associated with endometriosis in the ipsilateral ovary or other foci in the pelvis; this may result in tumor recurrence, either as borderline tumor or carcinoma.

This study has several limitations. One is that the follow-up period (median=6 years) is not long enough for borderline tumors given that one patient had recurrence 8 years after the initial surgery. A larger study of BSMT with a longer follow-up should be carried out. The accumulation of such studies will help elucidate the exact clinical features of this disease. Secondly, as mentioned previously, it was not possible to identify the mechanism of CA19-9 elevation. Finally, we only focused on clinical features of patients with BSMT, and no molecular analysis was performed. In previous studies, gene mutations of cancer-related genes, such as of KRAS proto-oncogene, GTPase (KRAS), AT-rich interaction domain 1A (ARID1A), and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations, were reported in BSMT, suggesting that molecular analysis may clarify the biological characteristics, development, and progression of this entity (4, 17, 18).

In summary, BSMT can occur in a wide range of age groups (19, 20), and it can be identified based on symptoms associated with pelvic masses or discovered incidentally without any symptoms (21, 22). The preoperative diagnosis of BSMT is often difficult because of variable clinical findings, but a history of endometriosis and elevated serum CA19-9 level may aid in some cases.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

Yoko Nagayoshi and Kyosuke Yamada designed this study. Yoko Nagayoshi wrote the initial draft of the article. Takafumi Kuroda and Daito Noguchi collected the data. Nei Fukasawa and Takako Kiyokawa reviewed hematoxylin and eosin-stained slides to confirm the histological type of tumors based on WHO 2020 criteria. Yoko Nagayoshi contributed to the analysis and interpretation of data and assisted in the preparation of the article. Aikou Okamoto critically reviewed the article and made revisions. All other Authors have contributed to data collection and interpretation and critically reviewed the article. All Authors approved the final version of the article and agreed to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgements

The article was edited by Enago (www.enago.jp) for English language review. The Authors would like to thank the staff of the Department of Obstetrics and Gynecology and Department of Pathology, The Jikei University School of Medicine Hospital for their support and cooperation.

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Received February 19, 2023
Revised March 4, 2023
Accepted March 6, 2023