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Original contribution

The presence and location of epithelial implants and implants with epithelial proliferation may predict a higher risk of recurrence in serous borderline ovarian tumors: a clinicopathologic study of 188 cases☆,☆☆

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Summary Serous borderline ovarian tumors have a favorable prognosis, and recurrences are uncommon. The factors influencing recurrence are not fully understood. Epithelial inclusions are identified in serous borderline ovarian tumors and are traditionally referred to as epithelial implants, which often show epithelial proliferation. We investigated whether the presence of epithelial implant and epithelial proliferation portends a higher risk for recurrence of serous borderline ovarian tumors in patients who underwent surgical removal of these tumors. Also examined was whether the anatomical site of epithelial implant and epithelial proliferation was associated with a higher risk of recurrence. One hundred eighty-eight cases of pure serous or predominantly serous borderline ovarian tumors were studied for the presence of epithelial implant and epithelial proliferation, and subsequent recurrences were recorded. The anatomical sites of epithelial implant and epithelial proliferation were compared between serous borderline ovarian tumors with or without recurrence. Statistical analysis was performed using the χ^2 test. Epithelial implant was noted in 106 cases (56%), and epithelial proliferation, in 26 cases (14%). Recurrence was identified in 10.4% cases with epithelial implant and 23% cases with epithelial proliferation. Statistical analyses of patients with recurrence showed significant differences in the following groups: epithelial implant versus no epithelial implant ($P < .025$) and epithelial proliferation versus no epithelial implant ($P < .001$). Recurrence rates were higher in the epithelial implant and epithelial proliferation groups as compared with no epithelial implant or epithelial proliferation groups. Epithelial implant and epithelial proliferation appear to pose a statistically significantly higher risk of

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recurrence in serous borderline ovarian tumors as compared with the absence of epithelial implant. Although the anatomical location of such implants was not significantly associated with a higher risk, the presence of epithelial proliferation at multiple sites was more frequently seen in recurrent serous borderline ovarian tumors.

1. Introduction

The subject of serous borderline ovarian tumors (SBOTs) of the ovary still raises questions regarding their biologic nature. This category of "borderline" or "low malignant potential" was created by the World Health Organization in 1973 [1]. The mortality from this disease is guided by the presence of extraovarian disease. The survival of women with extraovarian disease is reported to be approximately 70% [2]. The overall 5-year and disease-free survivals have been reported to be 98% and 87%, respectively, for stage 1 serous borderline tumors and 91% and 65%, respectively, for higher stage disease [3]. Long-term survival rates depend on the type of implants seen at presentation as well as the presence of progression to low-grade serous carcinoma [4,5].

The identification of "invasive implants" in SBOTs has been reported to be the most significant long-term prognostic indicator [6]. Invasive implants are considered biologically comparable with carcinomas, whereas noninvasive implants are currently believed to be benign. It has been proposed that some forms of noninvasive implants are derived from reactive mesothelial hyperplasia in situ, whereas others may represent true implants analogous to those that occur in endometriosis. SBOTs are often bilateral (25%) and can be associated with small papillary lesions in pelvic lymph nodes in approximately 20% to 40% cases [7].

A morphologic subset of serous borderline tumors, namely, the micropapillary subtype, has gained interest in the literature because of its association with (1) a higher frequency of extraovarian invasive implants, (2) low-grade serous carcinoma, and (3) on rare occasions, progression to high-grade serous carcinoma [8].

Micropapillary patterns of serous borderline tumors are often bilateral, exophytic, and associated with invasive implants [9]. Longacre et al [5] reported that the micropapillary pattern is associated with decreased overall survival on univariate analysis. However, this subtype did not have a significant adverse impact on overall survival when controlled for the presence of peritoneal implants. Micropapillary architecture and nondestructive stromal microinvasion in primary SBOTs were found to be predictive factors for disease progression over time. Stromal microinvasion was also found to be a predictor for disease progression, independent of stage [5,10].

Serous borderline tumors and low-grade serous carcinomas have a distinct molecular pathogenesis compared with high-grade serous tumors. BRAF and KRAS mutations are common in borderline tumors and low-grade serous carcinomas in more than 60% of cases [11,12]. These mutations are believed to occur in the early stage of tumor progression, for example, in the transformation from a serous cystadenoma to a more biologically malignant lesion. In high-grade serous carcinomas, p53 mutations are found in almost 100% of cases [13].

Most patients with serous borderline tumors have a favorable prognosis, and although recurrences do occasionally occur [5], they do not necessarily indicate progression to aggressive disease. Although it is known that the likelihood of recurrence is increased when a patient presents with high-stage disease, the specific risk factor(s) influencing recurrence is not completely understood.

It has been reported in the literature that epithelial inclusions, composed of single-layered cuboidal epithelial/mesothelial–type cells (sometimes with focal proliferation), can frequently be identified in the omentum [14]. These inclusions are also commonly encountered on the surfaces of the pelvic peritoneum, fallopian tubes, ovaries, and infrequently in the pelvic parietal peritoneum, omentum, and serosa of the bladder and bowel. Comparable extraovarian epithelial implants (EI) and implants with epithelial proliferation (PEI) are often encountered in cases of SBOTs. In this series, we investigated the presence of EI and PEI in patients diagnosed with SBOTs, focusing on anatomical location and multicentricity as potential risk factors for postoperative recurrence of these tumors.

2. Materials and methods

All cases of SBOTs diagnosed between January 1, 1991, and April 30, 2005, were retrieved from the pathology archives at the Women & Infants Hospital of Rhode Island (WIHRI), including both in-house and consultation cases for patients who received treatment at our hospital. Hematoxylin and eosin–stained original slides of all consultation cases were reviewed by senior gynecologic pathologists. Only fully staged consultation cases were included in the study. Some patients were staged by radiology, exploratory laparotomy, and surgery and managed by ovarian cystectomy or unilateral salpingo-oophorectomy when initially presented. Most retrieved cases were staged by the same cohort of gynecologic oncology surgeons at WIHRI, ensuring more consistent tissue sampling and nodal dissection procedures. All patients in this study were

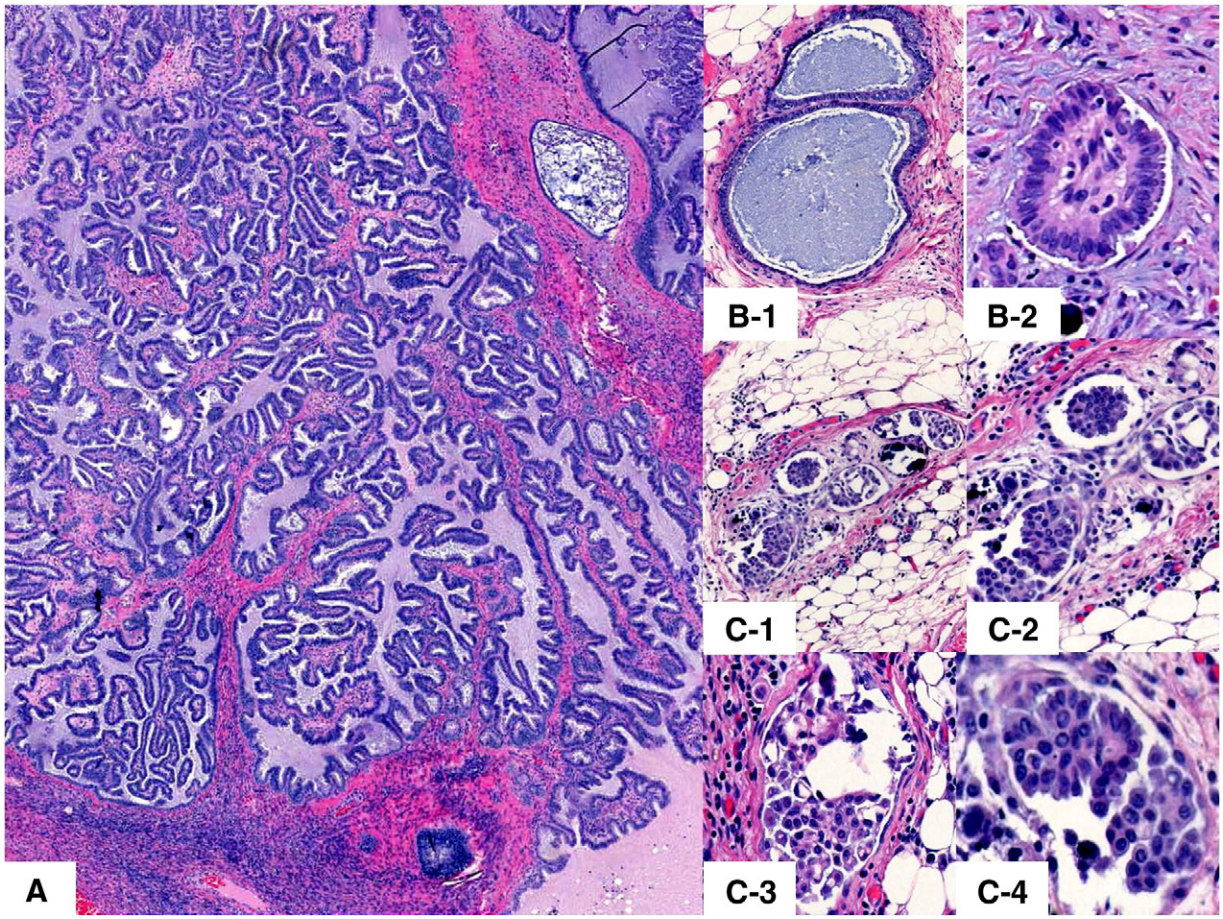

Fig. 1 Left column (A) shows low-power view of SBOT (H&E, original magnification ×2), right hand column upper row (B-1 [H&E, original magnification ×4] and B-2 [H&E, original magnification ×10]) shows EI, right column middle row (C-1 [H&E, original magnification ×4] and C-2 [H&E, original magnification ×10]) shows implants with PEI, and right lower row (C-3 and C-4 [both H&E, original magnification ×20]) shows PEI. H&E indicates hematoxylin and eosin.

managed and received follow-up at WIHRI. The presence of EI, PEI, and history of recurrence were recorded. The range, mean, and median duration of follow-up were recorded, and the *P* value was determined by the unpaired Student *t* test. The EI and PEI were defined by Bell and Scully [15] as follows: EI is lined by single layer of epithelium, whereas PEI exhibits papillarity and/or tufting. Fig. 1 depicts SBOT, EI, and PEI.

Table 1 Serous borderline tumors of the ovary

Total no. of primary serous BOT	188	
	With recurrence (n = 17)	With no recurrence (n = 171)
Absent EI (no EI)	0 [a]	56
EI	11 [a] (10.4%)	95
Implant with PEI	6 [a] (23%)	20

Abbreviation: BOT, borderline ovarian tumor.

[a] Statistical analysis showed the following significance: EI versus no EI, $P < .025$; PEI versus no EI, $P < .001$; EI versus PEI, $P \geq .05$ (not significant).

The following parameters were analyzed between patient groups with and without documented disease recurrence: (1) unilaterality versus bilaterality, (2) presence of concurrent EI and/or PEI, and (3) anatomical sites of EI and/or PEI (eg, ipsilateral and/or contralateral ovary, omentum, and pelvic lymph nodes). No cases with invasive implants were included in this study. In the subgroup with recurrent SBOTs, a χ^2 test was performed to examine the following histologic findings: EI versus no EI, PEI versus no EI, and EI versus PEI, with a *P* value cutoff of .05. The American Joint Committee on Cancer stage of the recurrent tumors was noted. Duration of follow-up for both recurrent and nonrecurrent groups of SBOTs was calculated. The recurrent and nonrecurrent groups were compared stage for stage, and the findings are tabulated in Tables 1 and 2.

All SBOTs were fully staged, diagnosed, and classified according to the criteria described in the current World Health Organization Classification scheme [16]. Serous adenofibroma with focal proliferation of epithelium was not included in the study, with application of the 10% cutoff criteria proposed by Seidman et al [17]. Also excluded were tumors with invasive implants, destructive stromal invasion, and

Table 2 Anatomical site involvement of EI and PEI and the recurrence SBOTs

	Bilateral BOT (%)	Ovarian surface involvement (%)	Ipsilateral ovary (%)	Contralateral ovary (%)	Omentum (%)	Omental noninvasive SBT implants (%)	Pelvic lymph nodes (%)
EI with recurrence (n = 11)	82 *	82 *	91 *	82 *	45 *	9 *	9 *
EI without recurrence (n = 95)	61 *	63 *	87 *	80 *	38 *	11 *	6 *
PEI with recurrence (n = 6)	100 **	100 *	100 *	100 *	100 *	100 **	33 *
PEI without recurrence (n = 20)	55 **	65 *	75 *	65 *	80 *	55 **	35 *

BOT indicates borderline ovarian tumor.
* $P > .05$.
** $P < .05$.

borderline tumors with microinvasion. The criteria originally proposed by Bell and Scully [15] were used to determine destructive stromal invasion and are summarized as follows: presence of individual cells or small clusters of eosinophilic cells or nonbranching papillae or cells with cribriform pattern within the stroma measuring less than 3 mm in maximum dimension. These microinvasive foci almost invariably have stromal retraction or clefts around them.

3. Results

A total of 188 cases of SBOTs were selected for the study. Of these, 56 cases (30%) did not show the presence of EI or PEI. EIs were noted in 106 cases (56%), and implants with PEI were noted in 26 cases (14%). These findings are summarized in Table 1. Statistical evaluation revealed the following P values for the patients with recurrence: EI versus no EI, $P < .025$; PEI versus no EI, $P < .001$; and EI versus PEI, P value, not significant.

The stratification of SBOTs was done according to the presence or absence of EI and PEI. The anatomical sites of involvement of EI and PEI were also noted, and their association with or without recurrent disease was tabulated. Statistical analysis was performed using χ^2 test. The findings are summarized in Table 2. Of the 17 recurrent tumors, 9 (53%) were stage I; 4 (24.5%), stage II; and another 4 (24.5%), stage III at presentation. Each of the 17 cases of recurrent SBOTs is detailed in Table 3.

All recurrent tumors in this series were SBOTs; no carcinoma was seen at recurrence. The duration of follow-up in the recurrent and nonrecurrent groups of SBOTs is shown in Table 4, and a 2-tailed unpaired Student t test showed $P = .215$ (not significant). The stage-for-stage

Table 3 Detailed presentation of recurrent SBOT tumors

Case no.	EI *vs* PEI	Initial surgical procedure	Site of recurrence	Pathology of recurrence	Initial stage by X-Lap/ radiology/surgery	Stage at recurrence	Time from initial diagnosis (mo)
1	EI	BSO	Small bowel wall	SBOT	1B	IIIC	264
2	EI	Unilateral salpingo-oophorectomy	Contralateral ovary	SBOT	1A	1B	108
3	EI	TAH-BSO, omental biopsy	Omentum	SBOT	1C	IIIA	40
4	EI	Ovarian cystectomy	Bilateral ovaries	SBOT	1A	IIB	178
5	EI	Ovarian cystectomy	Pelvis	SBOT	1A	IIC	78
6	EI	RSO, omental biopsy	Left ovary	SBOT	1A	1A	153
7	EI	Lt ovarian cystectomy, pelvic biopsies	Right ovary	SBOT	1A	1A	36
8	EI	Rt ovary cystectomy and Lt ovary and pelvic biopsy	Bilateral ovaries and pelvis	SBOT	1A	IIC	60
9	EI	RSO	Contralateral ovary	SBOT	1A	1A	82
10	EI	Left cystectomy	Left ovary	SBOT	1A	1A	51
11	EI	Bilateral cystectomy and omental BX	Omentum	SBOT	IIC	IIIA	49
12	PEI	Bilateral cystectomy	Bilateral adnexa	SBOT	1B	1B	38
13	PEI	Bilateral cystectomy	Pelvis	SBOT	1B	IIC	177
14	PEI	Rt ovary cystectomy	Bilateral ovaries	SBOT	1A	1B	72
15	PEI	RSO	Left ovary	SBOT	1A	1A	97
16	PEI	Rt ovary cystectomy	Right inguinal LN	SBOT	1A	IIIC	36
17	PEI	Bilateral cystectomy	Bilateral ovaries	SBOT	IIA	IIB	80

BSO indicates bilateral salpingo-oophorectomy; TAH, total abdominal hysterectomy; RSO, right salpingo-oophorectomy; Rt, right; Lt, left; Bx, biopsy; LN, lymph node.

Table 4 Duration of follow-up by recurrence

Duration of follow-up	With recurrence (n = 17)	With no recurrence (n = 171)
Mean [a]	99	108.9
Median	78	57
Range	36-264	7-221

[a] The 2-tailed unpaired Student *t* test showed $P = .215$ (not significant).

comparison between recurrent and nonrecurrent groups is shown in Table 5.

4. Discussion

More than 50 years after the creation of the category of SBOT by FIGO, the true biologic nature of these tumors still remains somewhat disputed in the pathology literature. Certain facts have been agreed upon by the pathology and gynecologic oncology community. Most of these tumors have an excellent prognosis, and recurrence is uncommon [18].

It is known that patients diagnosed with serous borderline tumors with invasive implants usually show recurrence and are subsequently treated by cytotoxic chemotherapy. In contrast, patients with SBOTs and noninvasive implants are not treated, but at times, their tumors may still recur. Sparse data are available in the literature addressing the risk factors for recurrence in serous borderline tumors. The prognostic value of recurrent serous borderline tumors associated with EI and PEI may be helpful in patient management. It is worth noting that we did not include any cases of invasive implants in this series.

In this study, when recurrence of SBOTs (stratified by the presence or absence of EI, PEI, and stage of initial disease presentation) was analyzed, the following results were noted: 0% of stage I patients without EI or PEI had recurrence, 10% of stage I patients with EI had recurrence, and 28% of stage I patients with PEI had recurrence. Insufficient cases of higher stage SBOTs were available in this series to make a statistically reliable assessment.

In this series, the mean follow-up was 99 and 108.9 months, respectively, in recurrent and nonrecurrent SBOTs, with a median of 78 and 57 months and a range of 36 to 264 months in the recurrent group and 7 to 221 months in the nonrecurrent group. The 2-tailed unpaired Student *t* test was not significant ($P = .215$).

The frequency of pelvic lymph nodal involvement by EI was found to be 9% in the group with recurrence and 6% without recurrence. This was not statistically significant. On the other hand, the nodal involvement by PEI was 33% and 35% with and without tumor recurrence, respectively; this was also not statistically significant. It appeared from this series that presence of EI or PEI in pelvic lymph nodes did not influence the recurrence of serous borderline tumors. It is of note that the incidence of epithelial inclusions in pelvic lymph nodes has been reported in the literature to be 11.4% [19]. EI was reported to be present in as high as 53% of lymph nodes in serous borderline tumors. In a separate study, the prognosis of serous borderline tumor with lymph node involvement was found to be excellent in patients without peritoneal disease [20].

In summary, the presence of EI and PEI appears to pose a statistically significant higher risk of recurrence in ovarian SBOTs as compared with the absence of EI. No statistically significant difference in recurrence was observed between the presence of EI and PEI. The anatomical site of involvement by EI and PEI did not pose a statistically significant higher risk for recurrence of SBOT. In those patients who had PEI at the time of the primary resection, there was an increased risk of recurrence ($P < .05$) if the patient had bilateral primary SBOTs accompanied by noninvasive omental implants. Presence of PEI involving multiple sites appears to pose a higher risk of recurrent SBOTs. The overall proliferative activity of the epithelium of the secondary Mullerian system may be an underlying risk factor for recurrent SBOTs. From this study, the presence of EI and PEI are independent risk factors for predicting recurrence in stage I SBOTs compared with the absence of EI.

Table 5 Recurrence of SBOT stratified by the presence or absence of EI, PEI, and stage of initial disease presentation

	SBOT (N = 188)					
	SBOT with EI (n = 106)		SBOT with PEI (n = 26)		SBOT with no EI or PEI (n = 56)	
	With recurrence	Without recurrence	With recurrence	Without recurrence	With recurrence	Without recurrence
Stage I (n = 171)	10	88	5	13	0	55
Stage II (n = 9)	1	3	1	3	0	1
Stage III (n = 8)	0	4	0	4	0	0
Stage IV (n = 0)	0	0	0	0	0	0

Zero percent of stage I without EI or PEI has recurrence.
Ten percent of stage I with EI has recurrence.
Twenty-eight percent of stage I with PEI has recurrence.

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