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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