Histologic Transformation of Benign Endometriosis to Early Epithelial Ovarian Cancer

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Between 1975 and 1990, 79 patients with Stage I epithelial ovarian cancer were treated at Massachusetts General Hospital. Patients were identified from the tumor registry and medical records were retrospectively reviewed. Pathological slides were evaluated for the presence of endometriosis, specifically looking for malignancy arising in endometriosis. Evidence of endometriosis was found in 22 of the 79 cases (28%). In the 23 cases of endometrioid histology, 9 cases (39%) were associated with endometriosis and, in the 17 cases of clear cell tumors, 7 (41%) were associated with endometriosis. All 8 cases of mixed histology had clear cell and/or endometrioid components and 4 cases (50%) were associated with endometriosis. Endometrioid adenocarcinoma accounted for 41% of the tumors associated with endometriosis, clear cell carcinoma 31%, mixed (endometrioid and/or clear cell types) 18%, and other types 9%. Among the 22 patients with associated endometriosis, we found 7 carcinomas (32%) arising in endometriosis. In these 7 cases a spectrum of benign and atypical endometriosis with a transition to clear cell or endometrioid adenocarcinoma were identified. These premalignant changes were characterized by cytologic atypia and architectural proliferation. Endometriosis was frequently encountered among patients with Stage I epithelial ovarian cancer of endometrioid and clear cell histologies. Endometriosis may play a role in the pathogenesis of some early stage malignant ovarian epithelial neoplasms.

INTRODUCTION

Endometriosis is defined as the presence of endometrial glands and stroma in ectopic locations. Endometriosis is a benign, but often progressive, disease that has an estimated 10% prevalence in the premenopausal population [1]. Only 2–4% of women with endometriosis are diagnosed in the menopausal period [2, 3].

Ovarian cancer causes more deaths than any other cancer of the female reproductive system [4]. Epithelial ovarian tumors account for 80–90% of all ovarian cancers [5]. It is estimated that 24,000 new cases of ovarian cancer will be diagnosed in 1994 in the United States and that there will be over 13,600 deaths [4]. Because of its intra-abdominal location and silent course, a late diagnosis with widespread carcinomatosis is a common presentation of this disease.

Sampson [6], in 1925, was the first author to describe a possible association between endometriosis and carcinoma of the ovary. Since then, several studies [7–18] have reported a potential malignant transformation of endometriosis in gonadal and extragonadal tissue. These authors have recommended strict criteria to define endometriotic lesions that may be premalignant. When using these criteria, only about 1% of all cases of endometriosis undergoes malignant transformation. This study was undertaken to evaluate the incidence of endometriosis with Stage I endometrioid and clear cell ovarian malignancies and to examine the possible role of malignant transformation of the endometriosis.

MATERIALS AND METHODS

Between 1975 and 1990, 79 patients with Stage I epithelial ovarian cancer were identified from the Massachusetts General Hospital Cancer Registry and their clinical records were reviewed [19]. Tumors of borderline malignancy were excluded from the study. Data, such as presence of endometriosis, demographic characteristics, medical history, symptoms at presentation, and diagnostic and therapeutic procedures, were recorded for each patient.

Of the 79 patients, pathologic material was available in 71, and all these cases were reviewed by one of the authors (JHE). Five to 69 (mean 31) hematoxylin and eosin-stained sections were reviewed per case. Each case was reviewed at least twice over a 3-month period. In cases where biopsy or excision was followed by a definitive staging procedure, the latter slides were also reviewed. In the 8 cases where archival material was not available for tumor typing and grading, data entered on the...
pathology were associated with time to disease recurrence and genital site. All 7 patients had tumors of endometrioid or clear cell histology. Some tumors had additional components. Among the 8 tumors with mixed histologies, 7 of the 17 (41%) clear cell tumors were associated with endometriosis. In addition, 4 more cases of endometrioid or clear cell lesions associated with endometriosis were among the 8 tumors with mixed histologies.

Endometriosis was defined as the presence of glandular epithelium accompanied by endometrioid stroma in a site other than the uterine corpus. The presence of unequivocal endometrioid stroma was considered sufficient when epithelium was absent or metaplastic (nonendometrioid) in type. The presence of hemorrhagic stroma, or stroma containing hemosiderin or hemofuscin, was considered helpful only in sites that were clearly separate from the tumor since intratumoral hemorrhage and cyst formation would be expected to result in a fibrous, hemosiderotic cyst wall even in the absence of endometriosis. The presence of histologic transformation from benign to malignant disease was necessary to consider malignant tumor to have arisen from endometriosis.

Staging was done retrospectively by the authors using the FIGO staging system for ovarian cancer [22] after a thorough review of pathology slides and reports as described above. Fisher’s exact test [23] and the Wilcoxon rank sum test [24] were used to compare patients with endometriosis to patients without endometriosis by demographic, historical, and therapeutic characteristics. Kaplan–Meier curves and the log rank test [25] were used to determine what characteristics were associated with time to disease recurrence and time to death.

RESULTS

During the 15-year time period (1975–1990), there were 79 patients with Stage I ovarian cancer. Endometrioid adenocarcinoma was the most frequently encountered histological subtype, accounting for 23 of the 79 tumors (29%), followed by mucinous 18 (23%), clear cell 17 (22%), serous 10 (13%), mixed 8 (10%), and malignant Brenner 3 (4%). Twenty-nine (37%) were grade 1, 28 (35%) were grade 2, and 22 (28%) were grade 3. Endometriosis was found in 22 of the 79 cases (28%). The 22 patients did not include any of the 8 patients where slides were unavailable. The median age of the 22 patients was 58 years (range 22–83) and 14 (64%) were nulliparous. Ten patients (45%) were premenopausal, 8 (36%) had associated hypertension, and 2 (9%) were obese.

Of the 22 patients with Stage I tumors associated with endometriosis, 41% were found in association with endometrioid histology, 32% clear cell, 18% mixed (endometrioid and/or clear cell), and 9% other subtypes (mucinous and malignant Brenner). Tumors associated with endometriosis were grade 1 in 50% of the cases, grade 2 in 32%, and grade 3 in 18%. Twelve of the 22 patients had Stage Ia tumor and 10 had Stage Ic. Evaluation of all the Stage I endometrioid and clear cell ovarian cancers, which presented over the 15-year period, revealed that 9 of the 23 (39%) endometrioid tumors and 7 of the 17 (41%) clear cell tumors were associated with endometriosis. In addition, 4 more cases of endometrioid or clear cell lesions associated with endometriosis were among the 8 tumors with mixed histologies.

Table 1 compares clinical and pathologic characteristics between patients with and without endometriosis. There were three recurrences (one in the pelvis, one in the upper abdomen, and one in the lungs) and deaths among the 22 women with endometriosis (14%) compared to six (11%) recurrences (three in the upper abdomen, one in the spine, one in the pelvis, and one in the lungs) and four (7%) deaths among the 57 women without endometriosis. The median time to recurrence for the two groups was 86 ± 6 and 91 ± 4 months, respectively (P = 0.82). The characteristics that were statistically different between the two groups were age and obesity. Patients without endometriosis were older and more likely to be obese. In addition, although not statistically significant, the women without endometriosis were more likely to be parous (P = 0.11).

Among the 22 patients with endometriosis, we were able to demonstrate that the malignancy arose from the endometriosis in 32% of the cases (7 cases). The patients were 27 to 69 (mean, 49) years old at presentation and 3 (43%) were premenopausal; 2 of the 7 also had benign endometriosis of the contralateral ovary and 2 patients had endometriosis at an extragenital site. All 7 patients had tumors of endometrioid or clear cell histology. Six of these seven tumors (86%) were grade 2 or 3, compared to four (27%) with grade 2 or 3 among those without identifiable premalignant changes (P = 0.01). In none of these cases was there a synchronous endometrial cancer. Four of the seven tumors were Stage Ic and three Stage Ia. One of the 7 women developed a pulmonary recurrence and died of her disease 42 months from diagnosis.

The transition from benign endometriosis to malignancy was characterized by cytologic atypia and/or architectural proliferation. The elements that suggested a premalignant transition differed among the seven cases. In two tumors (one endometrioid, one mixed endometrioid/clear cell), a prominent adenofibromatous or adenoacanthofibromatous component emerged within areas of endometriosis (Fig. 1). In three other tumors (two endometrioid, one clear cell), minor areas of glandular crowding and irregularity resembling endometrial hyperplasia, with at least nuclear atypia, were found within endometriotic foci (Fig. 2). In one of the endometrioid adenocarcinomas in the latter group,
intraluminal papillary tufting of atypical epithelial cells was focally conspicuous (Fig. 3). The final two cases were clear cell cystadenocarcinomas in which areas of endometriotic cyst lining separate from the tumor showed nuclear atypicality of glandular and surface epithelial elements (Fig. 4).

**DISCUSSION**

Malignant transformation of endometriosis is a rare but recognized complication of this disease. In 1925, Sampson [6] reported seven cases of ovarian carcinoma that he believed could have arisen from foci of endometriosis. In order to consider a carcinoma originating in endometriosis, he proposed the following criteria: (a) The presence of both malignant and benign endometrial tissue in the same ovary, (b) the demonstration of cancer arising in the ovarian endometriosis and not arising from elsewhere, and (c) the finding of tissue resembling endometrial stroma surrounding characteristic epithelial glands.

In 1953, Scott [7] suggested an additional qualification to complete Sampson’s criteria: the demonstration of a transition between benign endometriosis and malignant epithelium. Other authors [10–14] have recommended close scrutiny of cellular atypia and/or hyperplasia in ectopic endometrial tissue to define lesions that may be preneoplastic.

Over two-thirds of ovarian cancers are diagnosed in ad-

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<th>Without endometriosis</th>
<th>With endometriosis</th>
<th>P</th>
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<tr>
<td>Death</td>
<td>7% (57)</td>
<td>14% (22)</td>
<td>0.30</td>
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<td>Median time to death'</td>
<td>50 months (57)</td>
<td>88 months (22)</td>
<td>0.46</td>
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<td>Recurrence</td>
<td>11% (57)</td>
<td>14% (22)</td>
<td>0.48</td>
</tr>
<tr>
<td>Median time to recurrence'</td>
<td>56 months (57)</td>
<td>88 months (22)</td>
<td>0.82</td>
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<tr>
<td>Median age'</td>
<td>58 years (57)</td>
<td>51 years (22)</td>
<td>0.06</td>
</tr>
<tr>
<td>Parity &gt;0</td>
<td>53% (45)</td>
<td>33% (21)</td>
<td>0.11</td>
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<td>Obese</td>
<td>18% (51)</td>
<td>0% (21)</td>
<td>0.04</td>
</tr>
<tr>
<td>Grade 2 or 3</td>
<td>61% (57)</td>
<td>45% (22)</td>
<td>0.15</td>
</tr>
<tr>
<td>Median tumor size'</td>
<td>3.5 cm (44)</td>
<td>11.5 cm (20)</td>
<td>0.12</td>
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* Comparison was made with the Wilcoxon rank sum test. All other comparisons were made with Fisher’s exact test.
advanced stages [4]. Our study is composed of a rare subset of patients with Stage I disease. Interestingly, we found a high frequency of coexistent endometriosis within this cohort of 79 patients. An explanation for our findings would be the fact that endometriosis may be symptomatic, which may lead to an earlier diagnosis of this otherwise silent disease in early stages. In our series, 43% of women with endometriosis presented with pain which led to an evaluation and diagnosis of an ovarian malignancy. On the contrary, the majority of women with advanced ovarian cancer are relatively asymptomatic.

**FIG. 2.** Slight glandular crowding and irregularity in an endometriotic area adjacent to an ovarian cancer; atypical nuclei were rounded and vesicular (250×).

**FIG. 3.** Intraluminal papillary tufting and slightly atypical epithelial cells in an endometriotic area adjacent to ovarian cancer (290×).
The association between endometriosis and clear cell or endometrioid ovarian cancer is well documented. In general, endometriosis is associated with 30–40% of these histologies [17, 18], raising the question of whether endometriosis is a premalignant condition. In our study of patients with Stage I disease, endometriosis was associated with 39% of the endometrioid and 41% of the clear cell ovarian cancers. In the 7 of the 42 (17%) clear cell and endometrioid tumors (including two with mixed endometrioid/clear cell histology), a clear transition from benign to atypical to malignancy was documented.

In our study, strict criteria were used to define an endome-
triotic cyst that was contiguous or intimately associated with an ovarian tumor. Intratumoral hemorrhage and cyst formation (artifacts of rupture) and distention of adjacent hemorrhagic follicle cysts or atypical cortical inclusion cysts may all produce an appearance that mimics an endometriotic cyst. The use of strict criteria particularly applies to cystic endometrioid adenocarcinomas, which by their nature have neoplastic epithelium of an endometrial type and a component that may resemble endometrial stroma. In addition, a transition from benign endometriosis to malignancy with the presence of cytologic atypia and/or architectural proliferation had to be present in order to consider an endometriotic origin of the ovarian carcinoma.

In our study, seven patients were found to have a malignancy arising from endometriosis using these strict criteria. Fifteen other women were found to have cancer and endometriosis without identifiable evidence of premalignant changes. However, the precancerous stage may not have been histologically present because it may have already been destroyed by the tumor. These findings suggest that ovarian endometriosis may act as a precursor to certain types of ovarian carcinomas, specifically endometrioid and clear cell subtypes. A related issue is how to identify those endometriotic lesions that are potentially premalignant. Most other investigators have focused on Sampson’s [6] criteria with or without modification. Those criteria are only pertinent to evaluate if a malignancy arose from endometriosis. However, our criteria of cytologic atypia and/or architectural proliferation may be a way to identify endometriosis which in the future may undergo malignant change.

Several types of histologic changes were seen in the areas of transition. The most prominent findings for the endometrioid lesions included areas of glandular proliferation with crowding and irregularity resembling endometrial hyperplasia. Atypical epithelial cells with nuclear enlargement and hyperchromaticism were also important findings present in the areas of transition. These atypical cells with cytoplasmic clearing were more characteristic within the clear cell histology.

The 22 tumors associated with endometriosis had a clinical outcome similar to those without endometriosis. There were no statistical differences with respect to recurrence or survival. The seven tumors that appeared to arise from endometriosis are of higher grade (86% grade 2 or 3) than those without premalignant changes (27% grade 2 or 3). This was statistically significant ($P = 0.01$); however, the clinical outcome between these two groups did not differ and this may reflect the small sample size.

The current recommendations for estrogen replacement therapy in patients with a history of epithelial ovarian cancer are based on a retrospective review by Eeles et al. [26] of 373 women treated for ovarian cancer. These authors found no difference in overall or disease-free survival among patients receiving estrogen replacement therapy versus those who did not receive hormones, after consideration of other confounding factors. Reimnitz et al. [27] reported two cases of malignancy arising from a focus of endometriosis after surgical castration and unopposed estrogen replacement therapy. The authors of this last study recommended the use of progestins in replacement therapy to reduce the risk of malignancy arising in endometriosis. Our study does not specifically address this issue because none of our patients with ovarian cancer and associated endometriosis were taking unopposed estrogen. Based on the study by Reimnitz et al. [27], we feel that if estrogen replacement therapy is prescribed in this group of patients, progestins should also be given.

Endometriosis was frequently encountered among patients with Stage I epithelial ovarian cancer of endometrioid and clear cell histologies. A variety of lesions that might have premalignant potential were found when evaluating the pathologic slides in some of these patients. Our study and others suggest that some patients with endometriosis may be at risk of developing ovarian malignancies. Further studies attempting to identify those patients with endometriosis that are at greatest risk of developing a malignancy are warranted. Excision of endometriotic implants and endometriomas with careful histologic evaluation to characterize cytologic atypia or architectural proliferation may help in identifying which lesions are truly premalignant.

REFERENCES


