Anatomic Pathology / Endometrial Debris in Pap Smears

Degenerative Necrotic Endometrial Debris in Papanicolaou Smears

The Role in the Prediction of Endometrial Pathology

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Key Words: Endometrial neoplasms; Cervical smears; Role; Predictions; Pathology

Abstract

A retrospective review was done to evaluate the importance of degenerative endometrial debris accompanied with benign-looking endometrial cells in Papanicolaou (Pap) smears. In total, 306 patients were divided into 2 groups according to the absence (group 1) or presence (group 2) of endometrial debris. Eighty-one (26.5%) patients received histologic follow-up. The biopsy rate for premenopausal patients in group 2 was the highest (24/48 [50%]). Multivariate analysis showed that presence of endometrial debris rather than menopausal status was more related to the biopsy procedure. Malignancy was found more often in group 2 (16/39 [41%]) than in group 1 (2/42 [5%]). A malignant result was also more closely related to endometrial debris rather than menopausal status. Thus, we suggest that benign endometrial cells in Pap smears should be reported and the presence of degenerative endometrial debris is important. Patients with degenerative endometrial debris need comprehensive evaluation, regardless of menopausal status.

The Papanicolaou (Pap) test has been used for the detection of cervical squamous premalignant and malignant lesions for more than 60 years. The screening program has proven successful in reducing the incidence and mortality of cervical cancer.1,2 Unfortunately, the incidence of endocervical or endometrial adenocarcinoma has paradoxically risen in these years. The Pap test has been thought to be unreliable in the detection of endometrial lesions.3 However, the presence of atypical endometrial cells has been reported to be associated with a higher rate of significant endometrial pathology and should lead to additional evaluation for the presence of endometrial disease.4,6 In addition, in other subgroups of asymptomatic noncycle premenopausal and postmenopausal women, benign endometrial cells in Pap smears might also be an indicator of endometrial pathology.7-11 The 2001 Bethesda System12 recommended the reporting of endometrial cells in women 40 years of age or older, regardless of menstrual status or clinical history, because the status and history are often incorrect.

The standard management of atypical glandular cells in Pap smears was identified in the 2006 consensus guidelines for the management of women with abnormal cervical screening tests.13 However, there is no consensus on the evaluation of asymptomatic or premenopausal women who had endometrial cells without atypia in their Pap smears. The significance of the presence of isolated histiocytes in Pap smears for predicting endometrial carcinoma is also controversial.14-17 In our previous study, we found that degenerative necrotic endometrial debris along the smearing direction in the background of Pap smears was composed not only of histiocytes but also of degenerative inflammatory and individual necrotic cells.6 Necrotic debris and phagocytosis were also frequent findings in endometrial adenocarcinoma.6 This kind of background...
pattern is not yet a real tumor diathesis because it lacks granular protein and lysed RBCs. Since then, we have become interested in the clinical significance of the presence of such degenerative necrotic debris accompanying bland-looking endometrial cells in Pap smears.

The purpose of this study was to determine the significance of degenerative necrotic debris and bland-looking endometrial cells in Pap smears by correlation with the following endometrial pathology. The relation to menopausal status was also evaluated. We hoped that we could provide some evidence to support a reasonable management suggestion for the subsets of patients with different cytologic morphologic features and the age groups with different risks for significant pathology.

Materials and Methods

A retrospective review was done of the archives of the Department of Pathology, Taipei Veterans General Hospital, Taipei, Taiwan, from January 2006 to December 2010. A total of 125,369 Pap smears were performed in this 5-year period. Among them, 306 negative smears (0.2%) with the presence of bland-looking endometrial cells were identified. All of these smears were conventional Pap smears. The patients were divided into 2 groups: 1, with the presence of only benign-looking endometrial cells with or without stromal cells in the smears; and 2, benign-looking endometrial cells admixed with degenerative necrotic debris containing individual necrotic cells, cell debris, histiocytes, inflammatory cells, and phagocytes. For patients in groups 1 and 2, endometrial sonography was done to evaluate endometrial thickness. Endometrial biopsy or curettage would be performed if necessary, eg, for thickened endometrium or postmenopausal bleeding and followed by staging surgery for malignant pathologic diagnoses.

The clinical information, such as age, menopausal status, use of hormone replacement therapy, use of tamoxifen, and presence of abnormal bleeding, was obtained from medical records. Pathology findings from endometrial biopsy were categorized as benign, premalignant (endocervical adenocarcinoma in situ, endometrial atypical complex hyperplasia), or malignant (adenocarcinoma).

Based on cytohistologic and available clinical data, we statistically analyzed the differences between types of endometrial cells and menopausal status by using the \( \chi^2 \) test and multivariate logistic regression. A \( P \) value of less than .05 was considered statistically significant.

Results

Among 306 patients with negative Pap smears with benign-looking endometrial cells, group 1 accounted for 226 cases (73.9%) and group 2 for 80 cases (26.1%). The age of patients ranged from 25 to 90 years (median, 48 years). As for menopausal status, 241 patients (78.8%) were premenopausal and 65 were postmenopausal (21.2%). Group 2 findings were more common in postmenopausal women (32/65 [49%]) than in premenopausal women (48/241 [19.9%]; \( P < .001 \)).

Of the 306 patients, 81 (26.5%) received histologic follow-up including endometrial sampling in accordance with
The difference in biopsy rate between groups 1 (42/226 [18.6%]) and 2 (39/80 [49%]) was significant ($P < .001$). In conjunction with menopausal status, the biopsy rate of premenopausal patients in group 1 was highest (24/48 [50%]), followed by postmenopausal patients in group 2 (15/32 [47%]), postmenopausal patients in group 1 (8/33 [24%]), and premenopausal patients in group 1 (34/193 [17.6%]). The difference in biopsy rates between groups 1 and 2 for premenopausal patients was statistically significant ($P < .001$), whereas for the postmenopausal patients, it was not ($P = .056$).

**Table 1** Distribution of Biopsy Rate

<table>
<thead>
<tr>
<th>Menopausal Status/ Endometrial Debris</th>
<th>No Biopsy</th>
<th>Biopsy</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopause</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent (n = 193)</td>
<td>159 (82.4)</td>
<td>34 (17.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Present (n = 48)</td>
<td>24 (50)</td>
<td>24 (50)</td>
<td></td>
</tr>
<tr>
<td>Postmenopause</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent (n = 33)</td>
<td>25 (76)</td>
<td>8 (24)</td>
<td>.056</td>
</tr>
<tr>
<td>Present (n = 32)</td>
<td>17 (53)</td>
<td>15 (47)</td>
<td></td>
</tr>
</tbody>
</table>

* Data are given as number (percentage) unless otherwise indicated.

**Table 2** Multivariate Logistic Regression for Biopsy Procedure

<table>
<thead>
<tr>
<th>Relative Risk (95% Confidence Interval)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of endometrial debris</td>
<td>4.0 (2.3-7.1) &lt;.001</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>1.1 (0.6-2.2) .674</td>
</tr>
</tbody>
</table>

In 18 (22%) of 81 cases, there was premalignant or malignant pathology, including 14 endometrial endometrioid adenocarcinomas, 1 primary peritoneal serous carcinoma with endometrial seeding, 2 endometrial atypical complex hyperplasia cases, and 1 endocervical adenocarcinoma in situ. Of 42 group 1 patients, 2 (5%) had premalignant or malignant pathology, as did 16 (41%) of 39 group 2 patients. The difference was statistically significant ($P < .001$). The malignancy rate in postmenopausal women in group 2 was highest (8/15 [53%]), followed by premenopausal patients in group 2 (8/24 [33%]), postmenopausal patients in group 1 (1/8 [13%]), and premenopausal patients in group 1 (1/34 [3%]). The difference of malignant results between groups 1 and 2 for premenopausal patients was statistically significant ($P = .005$), whereas for postmenopausal patients, it was not ($P = .144$). **Table 3**. Multivariate analysis showed that a malignant pathology result was significantly related to the presence of...
degenerative endometrial debris (group 2) not related to the menopausal status. Table 4.

Discussion

The predictive value of benign endometrial cells or background histiocytes for endometrial pathology in Pap smears has been a subject of controversy. Some studies have suggested a significant finding, but the others did not.7,11,14-17 The controversy is understandable because the biopsy rate and the yield of endometrial neoplasms in these cases were relatively low in the past. Browne et al18 found a 5-fold increase in the frequency with which endometrial cells were reported after the implementation of the 2001 Bethesda System, which subsequently resulted in a 1.3-fold increase in the biopsy rate (25.2%). We had a similar biopsy rate (~26%) in the present study. For patients in groups 1 and 2, we used sonography to evaluate endometrial thickness. Endometrial biopsy or curettage was performed if necessary, eg, for thickened endometrium or postmenopausal bleeding. The biopsy rate for group 2 (49%) was much higher than for group 1 (19.9%; \( P < .001 \)), indicating that the presence of degenerative endometrial debris (group 2) had more clinical significance for necessitating endometrial biopsy or curettage.

As we know, endometrial carcinoma is more common in postmenopausal women and relatively less seen in younger women. Similarly, degenerative endometrial debris, which was more commonly noted in postmenopausal (49%) than premenopausal (18.6%) women (\( P < .001 \)). Although the biopsy rate for premenopausal women in group 2 (50%) was slightly higher than for postmenopausal women (47%), the difference was not significant (\( P = .784 \)). In addition, the difference in biopsy rates between groups 1 and 2 was significant in premenopausal but not in postmenopausal women. In multivariate analysis, only the presence of degenerative debris along with endometrial cells but not menopausal status was significantly related to the necessity for subsequent biopsy procedures (Table 2). So, we suggest that regardless of menopausal status, the presence of benign endometrial cells with or without degenerative debris should be reported in the Pap smear results. It is important for decision making by clinicians.

The present study is the first comparing the significance between degenerative endometrial debris and menopausal status. As for the prediction of malignant pathology between menopausal status and degenerative endometrial debris (group 2), our results showed that malignancy rate in postmenopausal women in group 2 was highest (53%) and in premenopausal women in group 1 was the lowest (3%). The difference in malignancy results for premenopausal patients between groups 1 and 2 was statistically significant (\( P < .001 \)), whereas for postmenopausal women, it was not (\( P = .056 \)). In multivariate analysis, a malignant pathology result was significantly related to group 2 but was not related to menopausal status. Group 2 had 12.2 times the risk for malignant pathology as group 1 (\( P = .002 \); Table 4). Group 2 results were not only more clinically significant, but also had much more malignant pathology than group 1. Thus, we suggest that comprehensive evaluation for patients with group 2 findings was suitable. The significance of these kinds of histiocytes containing debris was also shown by Nguyen et al14 and Iavazzo et al.17 Patients with these findings should be managed more aggressively.

Our results point out that degenerative endometrial debris had a more important role in the detection of significant endometrial lesions. When benign-appearing endometrial cells are present in the Pap smear, degenerative necrotic debris is a significant risk factor for endometrial pathology, regardless of menopausal status. Although the cervical screening program is not designed to detect endometrial lesions, early detection of any such cases is possible and is a beneficial bonus for the patients because it identifies significant degenerative endometrial debris in the Pap smears. The importance of recognizing benign-looking endometrial cells and degenerative debris in the background was demonstrated in the present study. Further studies including more cases are needed to confirm our observations.

Table 4.

<table>
<thead>
<tr>
<th>Presence of endometrial debris</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of endometrial debris</td>
<td>12.2 (2.5-69.0)</td>
<td>.002</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>2.6 (0.8-8.7)</td>
<td>.125</td>
</tr>
</tbody>
</table>

References


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