Contribution of nuclear morphometric features to differentiation of atypical complex type endometrial hyperplasia and low grade endometrial carcinoma

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Summary
Objective: The differentiation of atypical complex type endometrial hyperplasia (ACEH) and low grade endometrial carcinoma (EC) may be problematic in endometrial biopsy materials. Desmoplasia and stromal invasion are diagnostic for EC but they are not always demonstrated in endometrial biopsies. In this study, we investigated the contribution of nuclear morphometry to distinction of ACEH and low grade EC.

Methods: Ten low grade EC and eight ACEH cases retrieved from the archives of the Department of Pathology. For each case at least 100 nuclei (totally 1000 for both groups) were selected using hematoxylen-eosine stained sections and evaluated by a computer assisted system. Measured nuclear morphometric features were nuclear area, nuclear perimeter, circular form factor, diameter equivalent circle, minimum feret, maximum feret, area convex hull, perimeter convex hull.

Results: There was no significant differences between these two groups for circular form factor (P=0.871). But all other morphometric features were statistically significant (P<0.05).

Conclusion: Our findings suggest that nuclear morphometric features may be used as an ancillary diagnostic tool in addition to conventional histopathological findings in borderline lesion. These findings should be confirmed with expanded case series.

Key words: Carcinoma; Endometrium; Hyperplasia; Morphometry

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Received: May 24, 2011
Accepted: July 9, 2011
Published online: August 10, 2011
DOI:10.5455/jeim.100811.hr.007

Introduction
Endometrial biopsy is used frequently in order to differentiate benign endometrial lesions from malignant [1]. Mostly there is no difficulty in that differentiation, but in some cases histological findings obtained from endometrial biopsy are not adequate in differential diagnosis. One of sample of these cases is differentiation of atypical complex type endometrial hyperplasia (ACEH) and low grade endometrial carcinoma (EC) [1, 2]. Desmoplasia and stromal invasion are diagnostic for EC but they are not always demonstrated in endometrial biopsies and absence of this cannot be interpreted as “non-invasive lesions”. The other most valuable features for adenocarcinoma are presence of generalized atypia, confluent glandular growth (glandular fusion), a cribriform architecture, an excessive papillary pattern, neutrophilic inflammation and the presence of clonal budding or proliferation [2]. Despite careful examination of all these criteria, a clear distinction cannot be made in some cases and these cases are reported with expression of uncertainty. However, this differentiation is important for management of patients [3]. So, reproducible and specific another valuable criterion has been needed for this distinction. In this study, we investigated the contribution of nuclear morphometric features to distinction of ACEH and low grade EC.

Materials and methods

Case selection
Ten low grade EC and eight ACEH cases (diagnosis confirmed with further hysterectomy materials) retrieved from the archives of the Department of Pathology, Gulhane Military Medical Academy, during the period from 1995 to 2007.

Morphometric analysis
For each case at least 100 nuclei (totally 1000 for both groups) were selected using hematoxylen-eosine stained sections and evaluated with a system composed of the following components: a personal computer running Microsoft Windows NT 4.0
Service Pack 6a operating system (Microsoft, Redmond, Washington, USA); a light microscope with motorized stage (Zeiss Axioscope, Zeiss, Gottingen, Germany); a frame grabber (Matrox Meteor, Quebec, Canada); a digital camera attached to the microscope (Sony AVT Horn 3 CCD, Tokyo, Japan); and a special image analyses software (Carl Zeiss Vision KS-400 version 3.0 for Windows, Oberkochen, Germany) (Fig.1). Nuclear area, nuclear perimeter, circular form factor, diameter equivalent circle, minimum feret, maximum feret, area convex hull, perimeter convex hull were measured. Description of these nuclear morphometric features were presented in Fig.2.

Statistical analysis

All data obtained from ACEH and low grade EC were compared. Significance of results was evaluated by independent samples t test.

Results

All cases (10 low grade EC and 8 ACEH) were firstly diagnosed with endometrial curettage materials and than hysterectomy were performed. Six of ten low grade EC cases were diagnosed as ACEH with suspicion for low grade endometrial carcinoma and remains were reported as low grade endometrial carcinoma in first endometrial biopsy materials. Three of 8 ACEH cases were reported as ACEH with suspicion for low grade endometrial carcinoma and 5 of them were diagnosed as ACEH.

When compared nuclear morphometric features of ACEH with low grade EC, nuclear area, nuclear perimeter, diameter equivalent circle, minimum feret, maximum feret, area convex hull and perimeter convex hull showed statistically significant differences (P<0.05 for all). But there was no significant differences between these two groups for circular form factor (P=0.871) (Table 1).
Figure 2. Descriptions of measured nuclear morphometric features.

Table 1. Detailed numeric values of geometric features of the study groups.

<table>
<thead>
<tr>
<th>Geometric features</th>
<th>Groups</th>
<th>n</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Error Mean</th>
<th>Sig. (P)</th>
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<tbody>
<tr>
<td>Perimeter</td>
<td>ACEH</td>
<td>1000</td>
<td>0.0999</td>
<td>0.0130</td>
<td>0.00130</td>
<td>0.001*</td>
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<td></td>
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<td>0.1103</td>
<td>0.0143</td>
<td>0.00143</td>
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<td>Area</td>
<td>ACEH</td>
<td>1000</td>
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<td>0.0001</td>
<td>0.00001</td>
<td>0.001*</td>
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<tr>
<td></td>
<td>low grade EC</td>
<td>1000</td>
<td>0.0007</td>
<td>0.0001</td>
<td>0.00001</td>
<td></td>
</tr>
<tr>
<td>Circular form factor</td>
<td>ACEH</td>
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<td>0.7770</td>
<td>0.0603</td>
<td>0.00603</td>
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<td></td>
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<td>Diameter</td>
<td>ACEH</td>
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<td>0.0034</td>
<td>0.00034</td>
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<td>0.0309</td>
<td>0.0037</td>
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<td>0.0424</td>
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<td>Area convex hull</td>
<td>ACEH</td>
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<td>0.0006</td>
<td>0.0001</td>
<td>0.00001</td>
<td>0.001*</td>
</tr>
<tr>
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<td>0.0007</td>
<td>0.0001</td>
<td>0.00001</td>
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<tr>
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</tr>
</tbody>
</table>

Std: standard; Sig: significance; ACEH: atypical complex endometrial hyperplasia; EC, endometrial carcinoma. *statistically significant.

Discussion

In this study, nuclear morphometric features of ACEH showed difference compared with low grade EC. Differentiation of these tumors is sometimes problematic during the examination of endometrial biopsy material with light microscope. But this differentiation is important for further patient management.

Morphometric measurements can discriminate little differences that can not be detected during the light microscopic examination [4]. Limited morphometric studies have been done in endometrial biopsies [5-12]. The most recent study was made by Hecht et al in 2005 [5]. Their study has resulted as histopathological criteria for diagnosis of endometrial intraepithelial neoplasia correlates well with objective morphometry and
successfully segregates patients into high and low cancer risk subgroups with better reproducibility than atypical hyperplasia diagnosis. In 2000, Mutter et al [6] studied clonal analysis and nuclear morphometry in a series of 93 endometrial tissues. The morphological features have been evaluated by subjective diagnostic classification and computerized morphometric analysis. Their results showed that computerized morphometry resolved these lesions into monoclonal and polyclonal subgroups with a high degree of accuracy and reproducibility.

Only three morphometric studies have been done to differentiate ACEH and low grade EC in literature. Zhou & Du studied morphometric features of four groups of endometrial proliferations: adenomatous hyperplasia (21 cases), atypical hyperplasia (13 cases), adenocarcinomas with superficially myometrial invasion (9 cases) and with deep myometrial invasion (8 cases) using morphometry in 1992 [7]. They concluded that morphometric features of atypical hyperplasia and well-differentiated adenocarcinomas were similar. Ausems et al investigated 42 endometrial curettages diagnosed as marked atypical hyperplasia (MAH) in 1985 [8]. Only 8 cases progressed to invasive carcinoma. In this study, by analysis of morphometric data set, a scoring scale was obtained. According to this scale, morphometric features can differentiate MAH progressed to invasive carcinoma from MAH without progression. In 1984, an article about using morphometry in diagnosis of endometrial hyperplasia and carcinoma has been published by Baak [9]. In this paper, it is denoted that morphometry can classify these lesions and especially in cases of doubt, this classification might have decisive importance.

According to our results, 7 of 8 nuclear morphometric features can help to conventional histopathology on differentiation of these lesions. Circular form factor shows the roundness of objects and only this geometric feature could not separate these lesions. This is meaningful because nuclei of endometrial carcinoma are oval-round and similarly when convert the nuclei from spindle to oval-round, endometrial hyperplasia called atypical. So, it is already expected that circular form factor could not separate these group of lesions.

As conclusion, our findings suggest that nuclear morphometric features may be used as an ancillary diagnostic tool to conventional histopathological findings in borderline lesion. As mentioned above, there are limited studies that investigate contribution of morphometry to differential diagnosis of ACEH and EC in endometrial biopsy materials. These findings should be confirmed with studies which has wider case series.

References