Diagnosis of Endometrial Stromal Tumors

A Clinicopathologic Study of 25 Biopsy Specimens With Identification of Problematic Areas

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Key Words: Endometrial stromal sarcoma; Biopsy detection

DOI: 10.1309/AJCPXD0TPYSNVI8I

ABSTRACT

Objectives: To assess the difficulties associated with diagnosing endometrial stromal tumors (ESTs) on endometrial biopsy.

Methods: We examined 25 endometrial biopsy specimens from 19 consecutive women diagnosed with either endometrial stromal nodule (n = 3) or endometrial stromal sarcoma (n = 16).

Results: Rereview of the biopsy specimens revealed a stromal fragment suspicious for an EST in 16, of which eight had received a benign diagnosis on initial review. Most ESTs had an aglandular stromal fragment that was 5 mm or larger. Stromal fragments of this size were not encountered in the control material. Problematic areas included highly cellular leiomyoma and a lack of attention to the stromal compartment.

Conclusions: Most endometrial stromal tumors present with large aglandular stromal fragments (≥5 mm). These fragments are large enough that difficulties in diagnosis appear to be due to a lack of attention to the stromal compartment.

Endometrial stromal tumors (ESTs) are rare mesenchymal tumors occurring primarily in the uterine corpus. They constitute less than 10% of all uterine malignancies and approximately 20% of all uterine sarcomas.1,2 They are the second most common uterine mesenchymal tumor after leiomyosarcoma. In the 2003 World Health Organization classification of tumors, they are divided into endometrial stromal nodule (ESN), endometrial stromal sarcoma (ESS), and undifferentiated endometrial sarcoma (UES).3 Both ESN and ESS are low-grade tumors composed of a monotonous population of cells with a delicate vasculature resembling normal proliferative phase endometrial stroma. The distinction between the two rests on the evaluation of tumor circumscription, both macroscopically and microscopically.4 On biopsy material, a diagnosis of EST is often used because tumor circumscription cannot be determined. The diagnosis of these tumors on
light microscopy is complicated by the presence of a number of variant forms, including smooth muscle differentiation, glandular and epithelial differentiation, and sex-cord differentiation. UES, meanwhile, is an aggressive neoplasm with extensive cell atypia and necrosis.

The most frequent presenting symptom for both ESNs and ESSs is vaginal bleeding. One-third to half of ESSs present with spread outside the uterus. The diagnosis of EST on uterine biopsy can be extremely challenging due to its resemblance to proliferative endometrial stroma. Correct diagnosis is, however, of great clinical importance. After tumor type has been established, stage of disease is the most significant prognostic factor.

ESTs are characterized by specific chromosomal and molecular alterations. The most frequent chromosomal rearrangement is a translocation between the short arm of chromosome 7 and the long arm of chromosome 17. This nonrandom t(7; 17) and its variants have been detected in 31% of the karyotypes reported to date, as summarized in a recent comprehensive review. The characteristic molecular alteration found in ESTs is the recurrent chromosomal translocation t(7;17)/(p15; q21), which leads to production of JAZF1-JJAZ1 fusion RNA. This fusion, between the juxtaposed with another zinc finger 1 (JAZF1) and the joined to JJAZ1 (JJAZ1) genes, leads to expression of a fusion protein that, in cultured human embryonic kidney 293 cells, leads to resistance to apoptosis and, when the unarranged JJAZ1 protein is suppressed, increased rates of proliferation. The JAZF1-JJAZ1 fusion transcript as well as the t(7; 17)/(p15; q21) has been detected by reverse transcriptase–polymerase chain reaction and fluorescence in situ hybridization in 76% of ESNs and 58% of ESSs (43/74). In one study, low levels of JAZF1-JJAZ1 fusion transcript messenger RNA, as well as its protein product, were detected in normal endometrial stromal cell lines and in normal late secretory endometrial tissues. In another study examining the frequency of gene rearrangements in 94 ESTs found that the JAZF1-JJAZ1 fusion transcript could be detected in 50% of ESNs (4/8) and 70% of ESTs (28/40). Several other fusion transcripts have been identified in ESTs, including transcripts involving the PHD finger protein 1 (PHF1), enhancer of polycomb 1 (EPC1), and 14-3-3 genes. In one study, low levels of JAZF1-JJAZ1 fusion transcript messenger RNA, as well as its protein product, were detected in normal endometrial stromal cell lines and in normal late secretory endometrial tissues. Low levels of fusion transcript were not observed in two other studies of normal endometrium.

The clinical presentation of ESTs can be subtle, and diagnosis depends on correct interpretation of endometrial biopsy material. We are unaware of any other study specifically examining the biopsy diagnosis of ESTs. The goal of this study was to (1) examine the diagnostic accuracy of ESTs in biopsy and curettage material with a focus on diagnostic discrepancies and (2) provide clinically useful recommendations regarding the histologic evaluation of biopsy material.

Materials and Methods

Ethical Approval and Patient Inclusion

Ethical approval for the study was obtained from the Stockholm ethical review board. Searches of the pathology database and cancer registry identified all patients diagnosed with a low-grade ESS or ESN over a 10-year period (n = 19). The electronic medical record was used to identify previous biopsies. A control group, consisting of 80 endometrial biopsy specimens for bleeding, was also evaluated. The control cohort consisted of 40 biopsy specimens with subsequent hysterectomy showing no evidence of an EST. Most of these biopsy specimens contained malignancy, and so an additional control group of 40 biopsy specimens with nonmalignant diagnoses and a minimum follow-up time of 42 months was included.

Histologic Criteria for EST

Original H&E slides were available for review in 21 cases. On biopsy material, a diagnosis of EST was typically recommended. The presence of neoplastic stroma could represent either material from an ESN or sarcoma, a distinction that typically can be made only after hysterectomy. These tumor fragments typically showed the characteristic small thin-walled arterioles seen in endometrial stroma. The tumor cells had small nuclei with condensed chromatin and an indistinct cytoplasm. The fragments were similar to endometrial stroma; however, two key differences were discerned. First, in comparison to adjacent fragments of benign endometrial stroma in the same material, these fragments were often separate and distinct, consistent with a separate neoplastic process. Second, the cellularity was often increased in the tumor tissue, giving it a tighter and denser appearance in relation to normal stroma. Fragments showing these characteristics were recorded as “suspicious for endometrial stromal tumor.” The size of the largest intact fragment was measured. Areas of unusual differentiation were also noted.

Clinical parameters such as age at biopsy and subsequent hysterectomy, indication for the biopsy (as recorded on the pathology requisition), and the original diagnosis were recorded.

Results

Patient Cohort

Nineteen patients were retrospectively identified for inclusion in this study. Parameters of the patient cohort are presented in Table II. Sixteen patients were diagnosed with ESS and the remaining three with ESN. In 17 patients, the final diagnosis was made after hysterectomy. In the remaining two patients, no hysterectomy was performed and the
diagnosis was based on biopsy material. The mean age at final diagnosis was 61 years.

Of the 19 patients included in this study, three underwent a hysterectomy without any endometrial biopsy, 10 had one endometrial biopsy, three had two biopsies, and three had three biopsies. The total number of endometrial biopsies performed in the patient group was therefore 25.

### Clinical Indication for Endometrial Biopsies

The indication for the biopsy was noted for each of the 25 biopsies (Table 2). The indications included bleeding (n = 14), fibroid uterus (n = 2), tumor (n = 5), and biopsies in which the indication could not be determined from the available records (n = 4).

### Histology of Endometrial Biopsy Specimens

Of the 25 biopsy specimens, the original histology was reported as malignant/ESS (n = 6), suspicious for malignancy/ESS/EST (n = 4), endometrial polyp (n = 4), benign (n = 3), necrotic tissue (n = 2), highly cellular leiomyoma (n = 2), products of conception (n = 2), simple hyperplasia (n = 1), and inadequate (n = 1) (Table 2).

Rereview of the original material could be performed in 21 biopsy specimens, of which 16 showed one or more fragments of aglandular stroma suggestive of the presence of the endometrial stromal tumor. The sizes of the largest aglandular stromal fragment ranged from 2 to 19 mm (mean, 9.6 mm). Small stromal fragments between 1 and 2 mm were seen in 19 of 80 (24%) control biopsy specimens. In addition, one control biopsy specimen (1/80; 1%) had an aglandular stromal fragment that was 4 mm.

Eight of the 16 biopsy specimens from the EST group had an original diagnosis of ESS, EST, malignant, or suspicious for ESS, indicating a diagnostic accuracy of 50% (8/16). The remaining eight biopsy specimens had a nonmalignant original diagnosis, including highly cellular leiomyoma (n = 2), necrosis (n = 2), polyp (n = 2), simple hyperplasia (n = 1), and benign (n = 1). In four of these eight nonmalignant biopsy specimens, the original histology was reported as malignant/ESS (n = 6), suspicious for malignancy/ESS/EST (n = 4), endometrial polyp (n = 4), benign (n = 3), necrotic tissue (n = 2), highly cellular leiomyoma (n = 2), products of conception (n = 2), simple hyperplasia (n = 1), and inadequate (n = 1) (Table 2).

### Table 2

#### Summary of Endometrial Biopsy Material

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at Hysterection, y</th>
<th>Indication</th>
<th>Largest Stromal Fragment, mm</th>
<th>Original Diagnosis</th>
<th>Review Diagnosis</th>
<th>Time to Hysterectomy, mo</th>
<th>Hysterectomy Diagnosis</th>
</tr>
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<tbody>
<tr>
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<td>82</td>
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<td>2</td>
<td>Polyp</td>
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<td>0</td>
<td>ESS</td>
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<td>2</td>
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<td>2</td>
<td>Polyp</td>
<td>Polyp</td>
<td>87</td>
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<tr>
<td>3</td>
<td>45</td>
<td>Unavailable</td>
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<td>Benign</td>
<td>Benign</td>
<td>51</td>
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</tr>
<tr>
<td>4</td>
<td>52</td>
<td>Bleeding</td>
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<td>POC</td>
<td>POC</td>
<td>46</td>
<td>ESS</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
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<td></td>
<td>POC</td>
<td>POC</td>
<td>161</td>
<td>ESN</td>
</tr>
<tr>
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<td>39</td>
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<td>EST</td>
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<td>ESS</td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>Unavailable</td>
<td>2</td>
<td>Simple hyperplasia</td>
<td>Malignant</td>
<td>58</td>
<td>ESS</td>
</tr>
<tr>
<td>8</td>
<td>40</td>
<td>Fibroid uterus</td>
<td>12</td>
<td>Malignant</td>
<td>EST</td>
<td>1</td>
<td>ESS</td>
</tr>
<tr>
<td>9</td>
<td>38</td>
<td>Fibroid uterus</td>
<td>13</td>
<td>Suspicious for ESS</td>
<td>EST</td>
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<td>ESS</td>
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<tr>
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<td>Bleeding</td>
<td>17</td>
<td>Cellular leiomyoma</td>
<td>EST</td>
<td>13</td>
<td>ESS</td>
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<tr>
<td>11</td>
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<td>Benign</td>
<td>Benign</td>
<td>6</td>
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<tr>
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<td>33</td>
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<td>14</td>
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<tr>
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<td>90</td>
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<td>5</td>
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<td>Inadequate</td>
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<tr>
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<td>70</td>
<td>Bleeding</td>
<td>7</td>
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<td>EST</td>
<td>2</td>
<td>ESS</td>
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<tr>
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</tr>
<tr>
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<td>Bleeding</td>
<td>16</td>
<td>Necrosis</td>
<td>Necrosis</td>
<td>2</td>
<td>ESS</td>
</tr>
<tr>
<td>19</td>
<td>7</td>
<td>Bleeding</td>
<td>5</td>
<td>Suspicious for malignancy</td>
<td>Necrosis</td>
<td>2</td>
<td>ESS</td>
</tr>
</tbody>
</table>

ESN, endometrial stromal nodule; ESS, endometrial stromal sarcoma; EST, endometrial stromal tumor; POC, products of conception.
specimens, the patient had a hysterectomy in four months or less. In the other four cases, the time to final diagnosis was longer (13 months, highly cellular leiomyoma; 19 months, highly cellular leiomyoma; 53 months, endometrial polyp; and 58 months, simple hyperplasia).

Histologic examination of the biopsy specimens demonstrated a wide variation in morphology for these tumors. The most common morphology was the presence of intact fragments of aglandular stroma Image 2A. This pattern was seen in 10 of the 16 specimens, including one in which the specimen demonstrated myometrial infiltration.

Other patterns seen included a storiform pattern, characterized by more tumor cells with a spindle cell shape showing a slightly fascicular growth pattern (n = 2) Image 2B, a biphasic pattern with perivascular edema, characterized by alternating dense and loose areas of tumor resembling endometrial stroma, where the loose stroma typically had a central blood vessel (n = 1) Image 2C, a histiocytic pattern, where
Image 2: Histology of endometrial stromal tumors encountered in this study. A, Compact aglandular stroma showing whorling around small capillaries and a lack of cytologic atypia. B, Storiform growth pattern showing a spindle cell morphology and a haphazard growth around vessels. C, Biphasic pattern showing distinct perivascular pattern resembling edema. D, Histiocytic pattern where foamy cells give a "starry night" appearance. E, Crystalline material observed in one case. F, Decidua-like pattern with small cells with prominent eosinophilic cytoplasm. Scale bars and magnification: 20 μm, ×400 (A, C, D, F); 25 μm, ×200 (E); 50 μm, ×100 (B).
foamy stromal cells were seen throughout the tumor tissue (n = 1) Image 2D; a nodular pattern with eosinophilic crystalline material (n = 1) Image 2E; and a decidua-like pattern showing epithelioid cells with abundant cytoplasm (n = 1) Image 2F.

Discussion

ESTs are rare tumors, constituting only 20% of uterine sarcomas. The histologic appearances seen on the biopsy specimens in this study were similar to the variations in morphology seen in prior studies. Of greatest clinical concern is the misdiagnosis of an EST as a benign entity. This may lead to a delay in diagnosis with a subsequent increased risk to the patient of tumor spread at the time of (eventual) tumor presentation. Tumor stage at diagnosis is one of the most important prognostic indicators for these tumors.

One question addressed by this work relates to the subtlety of tumor presentation on the biopsy material. Of the 16 biopsy specimens with tumor, 13 had tumor fragments that were 5 mm or larger. This is in contrast to the control material, in which no biopsy specimens showed a stromal fragment that was 5 mm. The presentation of EST on the biopsy material is typically not as tiny fragments. In other words, the misclassification related more to the misclassification of tumor that was seen rather than missing small fragments. Smaller fragments of stroma, especially in the 1- to 2-mm range, but occasionally even up to 4 mm, can be due to benign causes, such as a submucosal leiomyoma attenuating the overlying glands or a stromal-predominant endometrial polyp. The presence of small stromal fragments (≤4 mm) does not appear to be specific for an EST. Larger stromal fragments (≥5 mm) were not encountered in the control material and appear to be more specific for an EST. Although large stromal fragments are suspicious for a stromal tumor, clinical and radiologic correlation is necessary.

The benign diagnoses that were confused with ESTs, based on our review, included highly cellular leiomyoma, “necrosis,” endometrial polyp, simple hyperplasia, and “benign.” The diagnosis of highly cellular leiomyoma should be made with care on biopsy material. Highly cellular leiomyoma is a tumor that has significant morphologic overlap with ESTs. Both highly cellular leiomyoma and early stage endometrial sarcoma or stromal nodule form a uterine mass and would be difficult to separate preoperatively through, for example, more exhaustive imaging or hysteroscopy. Previous work on hysterectomy material has described the following morphologic features of highly cellular leiomyoma: a focal spindle cell pattern, large caliber vessels with thick muscular walls, a gradual “merging” of the neoplastic cells with the surrounding myometrium, the presence of cleft-like spaces, the absence of foamy histiocytes, and diffuse desmin positivity. The application of these criteria is restricted in biopsy material. Immunohistochemistry for H-caldesmon has been shown to be of use in this differential diagnosis, but positive staining is typically found in only up to 75% of cells, as evaluated in hysterectomy material. A negative H-caldesmon in a biopsy fragment, therefore, does not exclude a highly cellular leiomyoma. In women who are postmenopausal or have completed childbearing, a hysterectomy for complete evaluation of the tumor may be indicated. In the two cases reported here, both showed a thin-walled vascular pattern that, in retrospect, supports identification of the tumor fragments as endometrial stromal in nature.

On rereview, the biopsy specimen diagnosed as “necrosis” showed tissue fragments that, although inflamed and partially degenerated, were not truly necrotic. The diagnosis of necrosis was sufficient to motivate close follow-up and eventual hysterectomy. The case diagnosed as endometrial polyp did have an endometrial polyp, but there was a separate tumor fragment that may have been overlooked on original review.

In the biopsy specimen originally diagnosed as simple hyperplasia, the 2-mm aglandular stromal fragment was separate from the surrounding endometrial fragments and showed a much denser stroma compared with other stromal fragments in the same material. Indeed, one of the most practical results of this work was observing that subtle tumor fragments can be identified through comparison with normal stroma in the same material.

The primary limitation of this study was that it is retrospective in nature. Although we have identified various morphologic clues that may assist in the diagnosis, it is unclear without a prospective study how useful these clues will be in clinical practice. These tumors are sufficiently rare that a prospective study is not feasible.

In summary, several clinically useful conclusions can be drawn from this work. First, most tumor fragments were 5 mm and larger and distinct from nearby fragments of benign stroma. This is in contrast to the control group, where the largest stromal fragment encountered measured 4 mm and was seen in only one of 80 cases. Second, most biopsy cases showed unusual differentiation. These two conclusions indicate that careful evaluation of endometrial stroma and comparison with background stroma should allow a stromal tumor to be identified. Cases with small fragments are probably too subtle to be identified in a prospective setting without a clear clinical suspicion, but these cases represent the minority. Unusual differentiation in a low-grade neoplasm should raise the suspicion of an EST. Further useful conclusions from this work are that the diagnosis of highly cellular leiomyoma should be made with caution on biopsy material, and in a postmenopausal woman, a hysterectomy should be considered in such cases to allow complete evaluation of the tumor. Additional diagnostic
discrepancies included polyp and simple hyperplasia. This would indicate that care should always be taken to evaluate the stromal compartment in these cases.

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Support for this project comes from Karolinska University Hospital Research, Development, and Education funds.

References


