Endometrial Stromal Sarcomas

Immunoprofile With Emphasis on HMB45 Reactivity

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Key Words: Endometrial stromal sarcoma; Stromal nodule; Immunohistochemistry; PEComa

ABSTRACT

Objectives: We describe the morphologic and immunohistochemical features of 17 endometrial stromal neoplasms, 16 sarcomas, and one stromal nodule.

Methods: We reviewed 35 cases interpreted as endometrial stromal neoplasms, but 17 high-grade endometrial stromal sarcomas (ESS) and one case of mixed endometrial sarcoma and leiomyosarcoma were excluded from the study. Data from the Surveillance Epidemiology and End Results program on low- and high-grade ESS for 1973 through 2003 were obtained.

Results: One uterine primary ESS had collections of clear cells (20%), while a metastatic ESS contained predominantly clear cells (90%). CD10 (88.2%) and smooth muscle actin (70.5%) were the most common positive immunohistochemical markers. The latter marker was located in the cytoplasm in 47% of the ESS and in the nucleus in 23.5%, a previously unreported feature. HMB45 was detected in 23.5% of the ESS, which contrasts with the 2% reported by other authors.

Conclusions: The presence of clear cells and HMB45 reactivity does not justify the term perivascular epithelioid cell tumors for these neoplasms. Two of 17 patients with ESS died of metastatic disease. However, among 274 cases of ESS (all stages included) collected by the Surveillance Epidemiology and End Results Program of the National Cancer Institute during a 30-year period, the 10-year survival rate was 94%.

Endometrial stromal neoplasms are characterized by a proliferation of cells with the phenotype of stromal cells of the proliferative endometrium. Traditionally, they have been divided into low- and high-grade endometrial stromal sarcomas (ESS). However, since high-grade ESS lack specific differentiation and bear no histologic resemblance to endometrial stromal cells, the designation of undifferentiated endometrial or uterine sarcomas has been proposed for these tumors.1 ESS are less common than high-grade ESS, accounting for only 0.2% of all genital tract malignancies and 15% of all uterine sarcomas and carcinosarcomas.2 Although the morphologic features of ESS have been studied extensively, their immunoprofile is less well known.

The purpose of this study was to describe the immunoprofile of 16 cases of ESS and one case of an endometrial
stromal nodule, with emphasis on HMB45 reactivity. We also emphasize the possible relationship of ESS to perivascular epithelioid cell tumors (PEComas) as well as the HMB45 reactivity in the former neoplasm and its possible clinical significance. The 10-year relative survival rate of 274 patients with low-grade ESS collected by the Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute during a 30-year period (1973-2003) was also analyzed.

Materials and Methods

We reviewed 35 cases interpreted as endometrial stromal neoplasms filed in the Department of Pathology of the National Cancer Institute of México City (n = 24), Medica Sur Hospital of México City (n = 4), National Institute of Medical Sciences and Nutrition of México City (n = 2), and personal consultation files of one of the authors (J.A.-S.) (n = 5). Sixteen cases of low-grade ESS and one endometrial stromal nodule were identified and selected for this study. Of these 16 cases, 11 were primary uterine neoplasms and five were metastatic deposits, of which three were located in the wall of the colon, one in the retroperitoneum, and one on the peritoneal surface. Seventeen cases of high-grade ESS and one case of mixed endometrial sarcoma and leiomyosarcoma were excluded from the study. Clinical and follow-up information was obtained from the medical records. Gross findings, including tumor size, location, and metastatic deposits, were obtained from pathology reports.

Multiple H&E-stained sections were available for review in all 17 endometrial stromal neoplasms. Likewise, paraffin blocks were available for all 17 neoplasms, and additional slides were prepared for immunohistochemical analysis. Immunostains were performed using the standard avidin-biotin peroxidase method. The following antibodies were studied

<table>
<thead>
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<th>Antibody Dilution and Source</th>
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<th>Clone</th>
<th>Dilution</th>
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<td>ASM/H120</td>
<td>1:50</td>
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<tr>
<td>HMB45</td>
<td>HMB45</td>
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<tr>
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<tr>
<td>Melan-A</td>
<td>M2-7C10</td>
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<tr>
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<td>RBT11</td>
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<tr>
<td>PR</td>
<td>RBT22</td>
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</table>

ER, estrogen receptor; PR, progesterone receptor; SMA, smooth muscle actin.

Data Source

Data were obtained from SEER for 1973 through 2003, using case listings as reported from 17 SEER registries. In 1973, SEER started with nine registries but in 2000 had expanded to 17, which covered approximately 26% of the US population. These years were selected to allow for at least 8 years of follow-up. In all, 274 cases of low-grade ESS (code 8931, *International Classification of Diseases for Oncology, 3rd ed*) were obtained.

Results

The age of the patients ranged from 38 to 75 years, with a mean of 50 years. Eleven patients with ESS had stage IC disease (International Federation of Gynaecology and Obstetrics) and five had stage IVB disease. Two of our 16 patients with ESS died of metastatic disease and five patients are living with metastatic disease. The 10-year survival of 274 patients (all stages included) collected by the SEER program was 94%. Figure 1 includes a comparison of the survival rate of low-grade ESS and high-grade stromal sarcomas collected by the SEER program.

Microscopic Pathology

At low magnification, all primary uterine and metastatic low-grade ESS were densely cellular and showed the characteristic tongue-like infiltrative pattern with prominent vascular permeation (Image 1). The cells were uniform, round, ovoid, or spindle-shaped, with no significant nuclear atypia or mitotic figures (Image 2). Clear cells predominated (80%) in one

![Image 1](https://example.com/image1)

![Image 2](https://example.com/image2)

Figure 1

Five- and 10-year relative survival of 274 patients with low- and high-grade endometrial stromal sarcoma (Surveillance Epidemiology and End Results Program, 1973-2003; all stages included). The blue bands represent the confidence intervals.
of the tumors and represented 20% of another tumor. Collections of foamy histiocytes were found in three ESS. The number of mitotic figures varied from zero to eight per 10 high-power fields. There were no multinucleated giant cells. Likewise, endometroid glands and sex cord–like structures were absent. A rich network of small arterioles resembling the spiral arterioles of the normal endometrium was seen in the stroma. A prominent hemangiopericytic pattern was noted in four tumors, and perivascular hyalinization was identified in five cases of ESS.

The endometrial stromal nodule had morphologic features similar to those of low-grade ESS, with the exception that it was well circumscribed and did not invade the myometrium or show vascular permeation.

Three metastatic lesions were located in the wall of the colon, one in the retroperitoneum, and one on the peritoneal surface. The architectural, cytologic (including the clear cells), and vascular features of these metastatic deposits were similar to those of the primary uterine tumors.

**Image 1** Low-power view of endometrial stromal sarcoma. The characteristic tongue-like pattern is seen (H&E; ×50).

**Image 2** High-power view of endometrial stromal sarcoma. The characteristic round uniform cells and the prominent arterioles are illustrated. Many of the cells show a clear cytoplasm (H&E; ×250).

**Image 3** Most neoplastic cells of this endometrial stromal sarcoma show a clear cytoplasm (H&E; ×300).

**Image 4** A well-demarcated stromal nodule contains numerous prominent arterioles (H&E; ×100).
The most common immunohistochemical markers in ESS were CD10 (88.2%) and smooth muscle actin (SMA) (70.5%), with cytoplasmic SMA detected in 47% and nuclear actin identified in 23.5%, followed by progesterone (64.7%) and estrogen (58.8%) receptors. HMB45 reactivity was present in 23.5% of the ESS while Melan-A was positive in 17.6% of the cases. All HMB45-positive cases also showed immunoreactivity for CD10. Three of the four HMB45-positive cases showed diffuse and strong reactivity.

Discussion

Low-grade ESS are distinctive mesenchymal uterine neoplasms, morphologically characterized by a tongue-like growth pattern with a prominent vascular permeation. The neoplastic cells are uniform and can be round, ovoid, or spindle shape; display the phenotype of the stromal cells of the proliferative endometrium; and show no significant nuclear atypia. A prominent vascular network composed of arterioles similar to those of normal proliferative endometrium was
present in all cases. Clear cells predominated in one of our 16 cases of ESS. Twenty percent of clear cells were present in another tumor. Foamy histiocytes were found in three tumors.

The histologic diagnosis of primary endometrial stromal tumors (stromal nodule and ESS) can be made with routine H&E-stained sections without difficulty. However, the identification of these tumors in metastatic deposits may be problematic. For example, the HMB45 positivity in one of our metastatic cases led to the erroneous diagnosis of malignant melanoma. Several studies have emphasized the usefulness of immunohistochemistry in the diagnosis of low-grade ESS, although the immunoprofile of these neoplasms lacks specificity.5-7 Our results essentially confirm previous immunohistochemical observations of ESS. The most sensitive immunohistochemical markers in our series were CD10 and SMA, followed by progesterone and estrogen receptors. Surprisingly, the SMA reactivity was detected in the cytoplasm of 47% of the tumors and in the nucleus in 23.5%, a previously unreported feature. It has long been recognized that the nucleus contains SMA filaments that have a variety of functions. Although the functions of nuclear actin have been a mystery for many years, it has been recently discovered that actin shuttles in and out of the nucleus through the action of transport receptors importin 9 and exportin 6, which are now recognized to function in the nucleus.8,9

HMB45 reactivity, the main focus of this investigation, has been found in a variety of malignant uterine neoplasms, including conventional leiomyosarcomas,10 leiomyosarcomas with clear cells,11 epithelioid leiomyosarcomas with clear cells,12 low-grade ESS,13 and the controversial tumors designated PEComas.14 The percentage of ESS that have expressed HMB45 has varied from 2% to 23.5%, with the reactivity more commonly focal than diffuse. In a large series of 397 uterine sarcomas studied by Abeler and Nenodovic,15 of the 84 ESS found, only 2% expressed HMB45, which is in contrast with our findings of 23.5%. This discrepancy may be due to the use of a different antibody clone or to ethnic and genetic differences of the patient populations.

Some investigators have emphasized the close similarities between PEComas and a subset of ESS with a predominance of clear cells. Vang and Kempson14 were the first to notice that four of the eight PEComas that they reported were similar to ESS. The World Health Organization monograph on gynecological tumors illustrated a low-grade ESS with clear cells and HMB45 positivity.1 We believe, however, that these tumors should not be included in the category of PEComas but rather as examples of low-grade ESS with clear cells and HMB45 expression. The HMB45 reactivity in our series of ESS did not alter the prognosis of these tumors. The patient with primary ESS and clear cells that expressed HMB45 was alive 8 years after diagnosis, and the other three patients with ESS and HMB45 reactivity were also symptom free more than 5 years after diagnosis. Since this is a small series, larger series with longer follow-ups are needed to confirm our observations. In our series, two of our 16 patients with ESS died of metastatic disease, and five patients are living with

![Table 2](image)

**Table 2**

Immunohistochemical Markers in 16 Cases of Low-Grade Endometrial Stromal Sarcoma and One Stromal Nodule

<table>
<thead>
<tr>
<th>Case No.</th>
<th>SMA Intensity</th>
<th>% in Cells</th>
<th>PR Intensity</th>
<th>% in Cells</th>
<th>ER Intensity</th>
<th>% in Cells</th>
<th>HMB45 Intensity</th>
<th>% in Cells</th>
<th>Melan-A Intensity</th>
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% Total of cases 70.5 64.7 58.8 23.5 17.6 88.2

ER, estrogen receptor; N, nuclear positivity; PR, progesterone receptor; SMA, smooth muscle actin; +, weak reactivity; ++, moderate reactivity; ++++, strong reactivity; –, negative.
metastasis. The 10-year disease-specific survival among 274 patients collected by the SEER Program, the largest series of these tumors, was 94%.

Even though many tumors show immunoreactivity for HMB45, most are smooth muscle neoplasms or neoplasms with a smooth muscle component. For example, in the uterus, most HMB45-positive neoplasms are leiomyomas or leiomyosarcomas with or without clear cells. The expression of HMB45 by ESS cells represents an exception in uterine tumors. The HMB45 positivity in angiomyolipomas of the kidney is seen in the smooth muscle cells. Likewise, the smooth muscle cells of lymphangioleiomyomatosis show immunoreactivity for HMB45. This antibody stains premelanosomes and immature melanosomes, which are not present in smooth muscle cells. The reason for the affinity of smooth muscle cells to HMB45 is unknown.

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References