Nonneoplastic Endometrial Signet-Ring Cells

Vacuolated Decidual Cells and Stromal Histiocytes Mimicking Adenocarcinoma

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Key Words: Signet-ring cells; Signet-ring cell adenocarcinoma; Endometrium; Decidua; Immunohistochemistry; Pseudoneoplastic; Histiocytes; Histiocytic; Muciphages

Abstract

We describe 5 patients (mean age, 50 years; all had uterine bleeding) whose routine endometrial biopsy and curettage specimens contained prominent signet-ring cells. Each specimen contained loose aggregates of signet-ring cells scattered within the endometrial stroma that were characterized by peripherally displaced, small, uniform nuclei with indistinct nucleoli and showed no mitotic activity. The central portion of the cytoplasm was occupied by single or multiple cytoplasmic vacuoles. In all cases, the signet-ring cells were reactive for vimentin and negative for epithelial membrane antigen and cytokeratin. Four cases were focally positive for muscle-specific actin or smooth muscle actin and negative for CD68, Mac387, periodic acid–Schiff, mucicarmine, and alcian blue. In these 4 cases, the surrounding endometrial stroma showed decidual changes, and the signet-ring cells demonstrated a morphologic continuum with more typical decidualized stroma. As such, the signet-ring cells in these cases were vacuolated, decidualized endometrial stromal cells. In the remaining case, the vacuolar contents of the signet-ring cells were periodic acid–Schiff–positive and resistant to diastase predigestion, and the cells reacted with Mac387 and CD68. The surrounding stroma showed no decidual reaction. Thus, the signet-ring cells in this case were of histiocytic differentiation. Endometrial stroma occasionally may contain nonneoplastic signet-ring cells that closely mimic adenocarcinoma. At least 2 directions of differentiation, decidual and histiocytic, are possible.

It is well recognized that poorly differentiated adenocarcinomas often accumulate mucin in large single or aggregated intracytoplasmic vacuoles that peripherally displace the nucleus and variably distort its contours into a crescent-shaped configuration. The result is a so-called signet-ring cell, a microscopic image once considered pathognomonic of a high-grade adenocarcinoma, usually of gastric, intestinal, or, less commonly, mammary or other origin. More recently, however, signet-ring cells or close mimics have been described in a variety of reactive or artifactual processes, as well as in occasional nonadenocarcinomatous neoplasms. In these instances, the cytoplasmic vacuoles have been empty or typically have contained materials other than epithelial mucin.

We describe the light microscopic and immunohistochemical features of 5 endometrial biopsy specimens containing signet-ring cells that strongly mimicked metastatic or primary adenocarcinoma. In 4 cases, the cells seemed to represent altered decidual cells, and in 1 case, the cells had features of histiocytes with phagocytic vacuoles. For comparison, the microscopic features of 2 signet-ring cell adenocarcinomas metastatic to the endometrium from the breast are presented.

Materials and Methods

During our routine practice, we encountered 3 of the present cases, all of which raised the strong possibility of metastatic adenocarcinoma to the endometrium and necessitated additional studies to exclude that possibility. Retrospective review of our files yielded 2 additional cases, as well as 2 cases of true signet-ring cell adenocarcinomas involving the endometrium. Our review did not include the evaluation of a
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series of sequential endometrial specimens; as such, determination of the incidence of signet-ring cell change in endometrial specimens could not be calculated from the present study. Clinical information and follow-up were obtained by review of the hospital charts. Tissues were fixed in 10% zinc-buffered formalin, routinely processed to paraffin embedding, and sectioned at 4 to 6 µm of thickness. All cases were stained with H&E, mucicarmine, periodic acid–Schiff (PAS) with and without diastase predigestion, and alcin blue. Immunohistochemical studies were performed using antibodies directed against cytokeratin (CAM 5.2, 1:4 dilution [Becton Dickinson, Franklin Lakes, NJ]; AE1/AE3, 1:50 dilution [Boehringer Mannheim, Indianapolis, IN]; and broad spectrum cocktail KC-21), epithelial membrane antigen (EMA; clone E29, 1:800 dilution; DAKO, Carpinteria, CA), vimentin (clone V9, 1:100 dilution; BioGenex, San Ramon, CA), muscle-specific actin (MSA; clone HHF35, 1:8 dilution; Enzo, Farmingdale, NY), smooth muscle actin (SMA; clone 1A4, 1:160 dilution; BioGenex), CD68 (clone KP-1, 1:200 dilution; DAKO), and antibody Mac387 (1:100 dilution, DAKO). Bound primary antibodies were localized using a standard biotin-streptavidin-horseradish peroxidase technique with 3,3’-diaminobenzidine tetrahydrochloride (DAB) as the chromogen. All immunohistochemical procedures were performed using an automated immunohistochemistry system (Ventana ES, Ventana, Tucson, AZ).

Results

Clinical Features

Pertinent clinical findings for the 5 women with nonneoplastic signet-ring cells in their endometrial biopsy specimens are summarized in Table I. The mean patient age was 50 years (range, 33-67 y). Three of 5 patients were postmenopausal. All 5 had either postmenopausal or intermenstrual, dysfunctional uterine bleeding. Two of 3 postmenopausal patients (cases 2 and 4) were being treated with progestogens at the time of biopsy. Dosages were in the standard ranges given for treatment of postmenopausal bleeding. Both of these biopsy specimens contained decidual-type signet-ring cells. The biopsy from the third postmenopausal patient (case 5), described as containing signet-ring cells with histiocytic features, was from a 52-year-old with no history of hormonal therapy. One patient (case 4) had a history of metastatic carcinoma of the breast, and a second (case 5) had a history of ductal carcinoma in situ of the breast.

For comparison with the aforementioned study cases, 2 endometrial biopsy specimens containing signet-ring cell adenocarcinomas were reviewed. The first was from a 66-year-old without a known history of a primary tumor outside the uterus. The second was from a 50-year-old with a 5-year history of infiltrating lobular carcinoma of the breast.

Histologic Observations

Nonneoplastic Signet-Ring Cells

In cases 1 through 4, the endometrium contained atrophic glands or glands with occasional secretory vacuoles associated with variable amounts of decidualized stroma and acute inflammation. Stromal necrosis was noted in 2 of 4 cases. Scattered within this background were loose aggregates of signet-ring cells having small, uniform nuclei and indistinct nucleoli. By visual inspection, approximately 5% to 10% of the stroma was occupied by signet-ring cells. These cells typically contained a single, large, empty-appearing cytoplasmic vacuole without septation. Mitotic figures were not identified. In all cases, the signet-ring cells were negative with PAS, mucicarmine, and alcin blue stains.

Case 5 also contained loose aggregates of signet-ring cells but had several distinct microscopic differences. The endometrium contained proliferative glands with no evidence of decidual changes or glandular atrophy as seen in the 4 previous cases. There was no necrosis or acute stromal inflammation. By visual inspection, the signet-ring cells occupied approximately 10% of the stroma, and individual signet-ring cells were not identified. In all 4 cases, the signet-ring cells were negative with PAS, mucicarmine, and alcin blue stains.

Table I

Clinical Features in Cases of Nonneoplastic Endometrial Signet-Ring Cells

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (y)</th>
<th>Menstrual Status</th>
<th>Hormonal Therapy</th>
<th>Symptoms</th>
<th>History of Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>Perimenopausal</td>
<td>None</td>
<td>Intermenstrual bleeding</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>Postmenopausal</td>
<td>Medroxyprogesterone, 10 mg</td>
<td>Postmenopausal bleeding</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>Premenopausal</td>
<td>None</td>
<td>Irregular bleeding</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>Postmenopausal</td>
<td>Megestrol, 40 mg, 4 times a day</td>
<td>Postmenopausal bleeding</td>
<td>Metastatic carcinoma, breast</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>Postmenopausal</td>
<td>None</td>
<td>Postmenopausal bleeding</td>
<td>Carcinoma in situ, breast</td>
</tr>
</tbody>
</table>
a spectrum of epithelioid cells ranging from those with prominent, nonvacuolated, eosinophilic cytoplasm to those that contained multiple, closely aggregated cytoplasmic vacuoles to cells with the classic signet-ring configuration of a single, large cytoplasmic vacuole and a displaced, distorted nucleus. In many instances, the vacuoles appeared to contain blue-gray mucin-like material. This material was weakly PAS positive and resisted diastase predigestion. Mucicarmine and alcian blue stains, however, were negative.

**Signet-Ring Cell Adenocarcinoma**

The first case consisted of markedly decidualized stroma with glandular atrophy consistent with exogenous progestogen effect. There were no areas of stromal necrosis or acute inflammation. A single fragment of endometrial stroma and underlying myometrium contained strands and cords of neoplastic cells with scattered signet-ring cells.

**Image 1** In cases 1 through 4, there were loose aggregates of signet-ring cells. **A**, These cells had small, uniform nuclei, indistinct nucleoli, and a single, large, empty-appearing cytoplasmic vacuole without septation (H&E, ×750). **B**, The signet-ring cells merged with less obviously vacuolated, more typical appearing decidualized endometrial stromal cells (H&E, ×250).

**Image 2** Case 5 also contained loose aggregates of signet-ring cells. **A**, While the majority of these cells contained multiple small cytoplasmic vacuoles, cells with a single large cytoplasmic vacuole and displaced nuclei also were identified (H&E, ×750). **B**, The background endometrium contained proliferative glands with no evidence of decidualization or glandular atrophy (H&E, ×250).
surrounding the neoplastic cells had a loose, areolar appearance, distinct from the appearance of the remaining endometrium. No decidualized cells or atrophic glands were associated closely with the area of adenocarcinoma. The neoplastic cells exhibited a spectrum of appearances ranging from cells with nonvacuolated eosinophilic cytoplasm to clear-cut signet-ring cells. Mitotic figures were not identified. The signet-ring cells were strongly positive for mucicarmine, which often highlighted a distinctly “targetoid” appearance.

The second case showed a typical postmenopausal pattern with weakly proliferative-appearing glands and prominent tubal metaplasia. There was no evidence of stromal decidual change. Scattered throughout the endometrium were neoplastic cells occurring singly and in small aggregates Image 3B. The cells had enlarged nuclei and variable amounts of cytoplasmic vacuolization, ranging from nonvacuolated cells to classic signet-ring cells. The cytoplasmic vacuoles contained blue-gray mucin-like material that stained strongly positive with mucicarmine and PAS.

**Immunohistochemical Observations**

The immunohistochemical features of the 5 endometrial biopsy specimens containing nonneoplastic signet-ring cells are summarized in Table 2. In all 5 cases, the signet-ring cells did not react for cytokeratin or epithelial membrane antigen but exhibited reactivity for vimentin. Cases 1 through 4 showed focally weak reactivity for MSA, SMA, or both, with negative reactivity for the histiocytic markers Mac387 and CD68 Image 4A. In contrast, case 5 demonstrated strong cytoplasmic positivity for CD68 and with Mac387 but lacked reactivity for SMA and MSA Image 4B. The 2 comparison cases of signet-ring cell adenocarcinoma involving the endometrium demonstrated strong positivity for cytokeratin Image 4C. Additional immunohistochemical studies were not performed on these cases.

**Discussion**

A signet-ring cell is defined by the presence of a large central cytoplasmic vacuole, aggregate of vacuoles, or an intracytoplasmic inclusion that pushes the nucleus to the periphery, at least partially distorting its contour into the shape of a crescent. Thus, the vacuole or inclusion becomes the “opening” in the ring, the surrounding cytoplasm forms the “body” of the ring, and the nucleus becomes the “stone.” Although once considered synonymous with adenocarcinoma, signet-ring cells are now known to occur in a variety of nonadenocarcinomatous neoplasms and in nonneoplastic processes.

More than a decade ago, Alguacil-Garcia documented signet-ring–like cells in the stroma of transurethral prostatectomy specimens. The vacuoles in these cells appeared to be empty spaces by electron microscopy, and they lacked staining for mucin. Staining for leukocyte common antigen and a strong association with the transurethral resection procedure suggested that these cells were reactive lymphocytes with artificial vacuoles. Subsequently, Randolph et al and Ro et al described signet-ring cell carcinoma of the prostate owing to cells with intracytoplasmic lumina and

![Image 3](image3.png) Signet-ring cell adenocarcinoma. **A**, In one case, the neoplastic cells formed strands and cords within the loose stroma (H&E, ×400). **B**, In the other case, the neoplastic cells were distributed singly or as small aggregates within weakly proliferative, postmenopausal pattern endometrium. In both cases, the tumor cells demonstrated a morphologic spectrum that ranged from nonvacuolated cells to classic signet-ring cells (H&E, ×400).
mucin-negative vacuoles. Similar signet-ring–like vacuolated cells also have been described in lymphomas, including mucosa-associated lymphoid tissue (MALT)–type lymphomas of the gastric mucosa.5,6 To add to the confusion with regard to gastric lesions, Zamboni et al7 described nonneoplastic epithelial cells representing altered lymphoepithelial lesions in patients with MALT lymphoma. In these cases, immunohistochemical reactions and mucin stains were not helpful in the differential diagnosis. However, close association with more conventional lymphoepithelial lesions and MALT lymphoma were useful diagnostic features. Intraglandular signet-ring epithelial cells may be encountered in inflammatory processes of the bowel, such as pseudomembranous colitis.7,8

Ramzy9 and others10 have described signet-ring stromal tumors of the ovary. In these cases, the mucin-negative cells seemed to result from hydropic swelling of mitochondria and intracytoplasmic inclusions.10 In 1996, Suster and Fletcher11 described prominent signet-ring cells containing glycogen in a small series of clinically benign gastrointestinal stromal tumors. Histiocytes have been documented to closely resemble signet-ring cells,12 particularly when they contain a variety of phagocytosed materials, such as the no-longer-used plasma substitute polyvinylpyrrolidone.13 The latter material is particularly treacherous diagnostically, because it stains strongly with mucicarmine.

Large intracytoplasmic aggregates of intermediate filaments in a variety of neoplasms including epithelioid sarcoma14,15 and malignant melanoma16,17 also may displace and distort the nucleus, creating a signet-ring–like appearance. Malignant melanoma also may contain vacuolated signet-ring cells.18 It can be argued that the cells with cytoplasmic inclusions are not true signet-ring cells because they lack cytoplasmic vacuoles. Nevertheless, the signet-ring appearance is often striking in such cases.

Signet-ring–like cells occasionally have been described in the endometrium, as well as in ectopic endometrial tissue. True primary signet-ring cell carcinomas of the endometrium are extremely rare but have been reported.19 Clement and Scully20 described an unusual postmenopausal decidual reaction of the endometrium. In 1 of their 4 cases, occasional decidual cells were noted to have a signet-ring–like appearance, analogous to those described in cases 1 through 4 of the present study. Paraffin blocks were not available for further evaluation of their case. Jacques et al21 reported 6 cases of unusual endometrial stromal cell changes, including signet-ring–like cells, that mimicked metastatic carcinoma. Before the study by Jacques et al,21 we had briefly described 4 cases of similar signet-ring–like decidualized cells.22

The present study expands on our previous work with histochemical and immunohistochemical characterization of the signet-ring cells, discussion of their pathogenesis, and comparison with metastatic signet-ring cell adenocarcinoma involving the endometrium. Signet-ring–like cells within ectopic decidua have also been noted in separate reviews by Clement et al23 and Clement and Young,24 and Nogales et al25 reported signet-ring–like cells in a single case of cesarean scar endometriosis with massive decidualization.

In the present study, nonneoplastic signet-ring cells were encountered in endometrial biopsy specimens in 5 patients. In 4 of these cases, the cells were associated with obvious decidualized stromal cells, and there was a morphologic spectrum from nonvacuolated to signet-ring cells. All 4 cases were negative for mucin markers and showed focal positivity for muscle markers, consistent with decidual cells. Case 5 lacked a decidual component and consisted of scattered signet-ring cells that reacted for the histiocytic marker CD68 and with Mac387. In addition, the signet-ring cells in this case were weakly PAS-positive and resisted diastase predigestion.

We believe that the present cases represent 2 distinctly different mechanisms for the development of nonneoplastic endometrial stromal signet-ring cells. In the first 4 cases, the cells seem to represent degenerating decidual cells. During decidualization, endometrial stromal cells have been documented to acquire cytoplasmic vacuoles secondary to the accumulation of glycogen and glycoproteins.26-28 The signet-ring cells described in the present study seem to be an exaggeration of this phenomenon. The lack of PAS staining may be due to the removal of any intravacuolar glycogen during tissue processing. In these cases, demonstration of a morphologic spectrum with more typical decidual cells, as well as

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**Table 2**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>EMA</th>
<th>CK</th>
<th>MSA</th>
<th>SMA</th>
<th>Vimentin</th>
<th>CD68</th>
<th>Mac387</th>
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<tr>
<td>1</td>
<td>–</td>
<td>–</td>
<td>Focal, weak</td>
<td>Focal, weak</td>
<td>++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>–</td>
<td>Focal, weak</td>
<td>Focal, weak</td>
<td>++</td>
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<td>–</td>
</tr>
<tr>
<td>3</td>
<td>–</td>
<td>–</td>
<td>Focal, weak</td>
<td>Focal, weak</td>
<td>++</td>
<td>–</td>
<td>–</td>
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<tr>
<td>4</td>
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<td>–</td>
<td>Focal, weak</td>
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<td>–</td>
<td>–</td>
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CK, cytokeratin cocktail; EMA, epithelial membrane antigen; MSA, muscle-specific actin; SMA, smooth muscle actin; +, positive; ++, strongly positive; –, negative.
lack of staining for mucin and immunohistochemical nonreactivity for epithelial markers, should allow recognition. The presence of decidua, per se, is not a helpful feature. One of our comparison cases with metastatic adenocarcinoma to the uterus demonstrated well-formed stromal decidual change in response to exogenous progestogens. Of note, the vacuolar contents of the signet-ring decidual cells in the present study, as well as those in a previous study of endometrial biopsy specimens, were negative for alcian blue; other authors, however, have described that the vacuoles contain acidic mucin, as indicated by alcian blue positivity. This apparent discrepancy may be because different cell types, with different synthetic capabilities, were being observed. Specifically, in the 2 studies, including the present study, in which the vacuoles were negative for alcian blue, endometrial biopsy specimens were studied, and the decidual signet-ring cells were endometrial stromal in origin. In contrast, the signet-ring cells in which acidic mucin was observed in the vacuoles were ectopic decidual cells of the submesothelial stroma. Ectopic decidual cells are derived from submesothelial stromal cells. Accordingly, eutopic and ectopic decidual cells arise from different cell types, endometrial stromal cells and submesothelial stromal cells, respectively. In turn, these different cell types likely have different synthetic capabilities, which would explain the apparent discrepancy in the vacuolar contents of the signet-ring decidual cells in the 2 sites.

The last case in our series contained signet-ring cells with often multiple, closely apposed cytoplasmic vacuoles, many of which seemed to contain blue-gray mucin-like material. This case lacked a background decidual component, and the vacuolar contents of the signet-ring cells were weakly PAS-positive and resisted diastase predigestion. These features increased the potential for confusion with
signet-ring cell adenocarcinoma. However, immunohistochemically, these cells expressed histiocytic markers and lacked epithelial markers. We have encountered similar muciphagic cells in colonic biopsy specimens. These cells also may be related to the cells of “signet-ring sinus histiocytosis.” Although the latter usually seem to consist of cells with empty cytoplasmic vacuoles, occasional cases have contained PAS-positive, diastase-resistant material.  

The endometrium should be added to the growing list of anatomic sites capable of harboring nonneoplastic signet-ring cells mimicking the cells of high-grade adenocarcinoma. At least 2 distinct mechanisms, a degenerative decidual change and accumulation of mucin within tissue macrophages, seem to account for the appearance of these cells. Exclusion of metastatic adenocarcinoma can be strongly supported in the former tumors when a spectrum of cytologic appearances, including blending with more typical decidual cells, is documented. If required for diagnosis, lack of immunohistochemical reactivity for epithelial markers is a key distinguishing feature for both variants. Mucin stains alone may compound the diagnostic confusion if the signet-ring cells represent muciphagic histiocytes.

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References


