Small Cell Carcinoma of the Uterine Cervix
Cytologic Findings in 13 Cases

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BACKGROUND. There are few reports on the cytologic features of small cell carcinoma (SMCC) of the uterine cervix.

METHODS. The clinical records, histopathology, and available cervical smears from all cases of SMCC of the uterine cervix in the files of the British Columbia Cancer Agency between 1985 and 1997 were reviewed.

RESULTS. Cervical smears were available from 11 of 13 identified cases. Six cases had a pretreatment smear containing numerous definitely malignant cells. In the seven cases with reported negative smears, review of the most recent smears detected a missed high grade squamous intraepithelial lesion in one case and rare suspicious epithelial cells in a second case. These two cases were considered to be false-negative smears on review. None of the six malignant smears were diagnosed as SMCC on cervical smears. These smears were reported as malignant epithelial cells, not otherwise specified in three cases and misclassified as adenocarcinoma in three cases. These malignant smears contained cells dispersed as single cells or arranged as loosely cohesive sheets or gland-like aggregates. Tumor cells, ranging from small to large, had extremely pleomorphic, angulated nuclei that were hyperchromatic and showed nuclear molding and smearing. Mitotic figures were common and karyorrhectic debris was identified in all cases.

CONCLUSIONS. The routine cervical smear is a relatively insensitive and nonspecific method of detecting SMCC. The specific diagnosis of SMCC on cervical smears is difficult. SMCC can mimic inflammatory cells, follicular cervicitis, endometrial cells, endocervical adenocarcinoma, squamous cell carcinoma of small cell type, non-Hodgkin’s lymphoma, and other unusual malignant neoplasms. The suspicion of SMCC on a cervical smear should prompt an urgent biopsy to establish the diagnosis and initiate prompt treatment. Cancer (Cancer Cytopathol) 1998;84:281–8. © 1998 American Cancer Society.

KEYWORDS: cytology, Papanicolaou smear, small cell carcinoma, neuroendocrine carcinoma, cervix, pitfalls.

Small cell carcinomas (SMCCs), which form part of the spectrum of neuroendocrine tumors of the uterine cervix and account for approximately 5% of invasive cervical carcinomas,1 have distinct clinical and histologic features.2–8 The majority of tumors present in a manner similar to that of squamous cell carcinoma of the cervix. Occasionally, paraneoplastic syndromes occur.9,10 The histopathology and biologic behavior of SMCCs resemble those of SMCC of the lung. The majority of reported patients have died of disease within 2–3 years of diagnosis.3–6,8

The few case reports that exist describing the cytologic features of SMCC on cervical cytologic smears (Papanicolaou smears)11–13 reflect, in our experience, only part of the cytologic spectrum of these tumors. Cervical smears have been noted to have a low sensitivity for
the detection of SMCCs. In 1 series of 14 cases, 6 patients had recent cervical smears that were reported as negative for malignancy. This article describes the cytologic findings, treatment, and outcome data of 13 cases of histologically confirmed SMCC.

MATERIALS AND METHODS

Sixteen cases of SMCC recorded between 1985 and 1997 in the computerized cancer registry files of the British Columbia Cancer Agency, a provincial cancer registry and treatment center, formed the basis of this study. The histologic sections of these cases were reviewed by the authors using recently defined criteria for the diagnosis of small cell carcinoma of the cervix. In brief, the criteria were: 1) a neoplasm comprised of small cells with scanty cytoplasm, nuclear molding, and indistinct nucleoli arranged in insular or trabecular growth patterns, in addition, > 10 mitoses per 10 high-power fields and single cell necrosis were present; 2) immunohistochemical differentiation; and 3) absence of or < 5% of squamous cell carcinoma or adenocarcinoma within the tumor. On review of the histology, 13 cases met the criteria and were included in the study. Two cases reclassified as large cell neuroendocrine carcinoma and one case reclassified as atypical carcinoid tumor were excluded from the study.

The patients’ cervical smears were traced from the computerized cytology files of the British Columbia Cancer Agency. All patients had ≥ 1 smears taken within 5 years of the diagnosis of SMCC. All available smears in this 5-year period were reviewed. In two cases slides originally interpreted as negative were not available for review, having been destroyed after being kept for 7 years. Slides from the remaining 11 cases were reviewed. From the six cytologically malignant cases, six slides reported as malignant and five slides (two cases) reported as negative were reviewed. From the 7 cytologically nonmalignant cases, 13 slides (5 cases) were available for review; 12 were reported as negative and 1 was reported as high-grade squamous intraepithelial lesion (HGSIL) (moderate squamous dyskaryosis). Slides were assessed for the following features: cellularity and cell arrangement including single cells, sheets, and clusters; nuclear features including nuclear shape, molding, nuclear smearing, chromatin staining, and nucleoli; nuclear/cytoplasmic ratio; mitosis; and nuclear debris.

All the smears were taken with an Ayres-type spatula from the squamocolumnar junction. The slides were stained in the laboratory of the British Columbia Cancer Agency using a modified Papanicolaou technique as described previously. The patients’ charts were retrieved from medical records and relevant clinical information extracted. The clinical stage of the tumors was recorded on the clinical record and followed the most recent International Federation of Gynecology and Obstetrics (FIGO) staging of carcinoma of the cervix uteri used at the time of diagnosis.

RESULTS

Clinical Findings

The clinical data of the 13 patients are summarized in Table 1. The patients’ ages at diagnosis ranged from 23–69 years; 7 patients were age < 40 years. Eleven patients presented with abnormal vaginal bleeding of variable duration (range of several weeks to 2 years). Two of these patients also had lower abdominal pain. Two patients presented with lower abdominal pain as the sole reported symptom. The tumor in one patient was detected on a routine prenatal examination. None of the patients presented with a paraneoplastic syndrome. Nine patients were FIGO Stage IB, two patients were Stage II, and two patients were Stage III.

All patients were treated initially with combination chemotherapy and regional external beam pelvic radiation. Seven Stage I patients received brachytherapy and two Stage I patients underwent an abdominal hysterectomy. One Stage II patient received brachytherapy and another Stage II patient underwent an abdominal hysterectomy. Two Stage III patients were treated with brachytherapy. Five patients also received prophylactic brain radiation, including three Stage I patients, one Stage II patient, and one Stage III patient. Three patients died of disease in < 2 years (range, 11 months–21 months). Ten patients were alive without disease with follow-up ranging from 2 months to 118 months, with three of these patients without recurrent disease > 8 years of diagnosis.

Histologic Findings

Two groups of SMCC were noted histologically based on the predominant cell size within the tumor and were designated as small cell type and intermediate cell type.

Histologically, eight cases were comprised predominantly of the intermediate cell type (Fig. 1). These cases showed tumor cells arranged in sheets and nests, with pseudosarose formation around stromal vessels and peripheral palisading of nuclei. Associated adenocarcinoma was present in two cases (one with in situ and one with invasive disease) and one case was associated with a uterine malignant mixed müllerian tumor. Subepithelial extension of malignant cells was noted in several cases (Fig. 2), although invasion through the cervical epithelial surface was present in all the biopsies.

The histology of five cases predominantly was that
of a dispersed pattern of small round tumor cells (Fig. 3). Clustered cells did not show rosettes or peripheral palisading. Tumor cells had scanty cytoplasm and round, hyperchromatic nuclei. Easily identified mitoses and single cell and confluent necrosis were noted.

Special studies including electron microscopy, silver stains, and immunostains were reported in a few cases but overall were considered too incomplete to include in this study.

**Cytologic Findings**

The original cytologic findings of the 13 cases of SMCC are summarized in Table 1. Although the diagnosis was suspected in one case, no case received a specific cytologic diagnosis of SMCC. Six cases originally were
interpreted as malignant and seven cases originally were interpreted as negative. Two of these cases had no slides available for review. The slides from three of these cases were found to be true-negative smears on review. On review of the most recent smears, the slides from two of these cases revealed a missed HGSIL in one case and rare malignant epithelial cells in the second case. These two cases were considered to be false-negative smears on review.

The cytologic features noted in our cases of SMCC are summarized in Table 2. The size and nuclear morphology of the malignant cells present in the smears could not be correlated with the two histologic subtypes of SMCC, possibly because there was only one case of the small cell variant of SMCC that had a positive smear.

The cervical smears from the intermediate cell histologic subtype originally were diagnosed as endocervical adenocarcinoma in three cases, malignant epithelial tumor not otherwise specified (NOS) in two cases, and negative in two cases. The slide from one negative case was reviewed as negative (true-negative) and the slides from the other negative case were not available for review.

The cervical smears from the small cell histologic subtype originally were diagnosed as malignant epithelial tumor NOS in one case and negative for malignancy in five cases. On review of the most recent slide from one negative case, rare cells were reinterpreted as HGSIL (moderate squamous dyskaryosis). On review of a second case, rare suspicious-appearing epithelial cells were found. Review of the two remaining negative smears found no abnormal cells (true-negative smears). One negative case had no slides for review.

Three patterns of distribution of malignant cells were identified with all smears showing more than one pattern. All smears contained malignant epithelial cells in the second case. These two cases were considered to be false-negative smears on review.

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Three patterns of distribution of malignant cells were identified with all smears showing more than one pattern. All smears contained malignant cells dispersed in a single cell pattern. Although malignant cytologic features were identified at high power, at scanning power some fields resembled exudate from follicular cervicitis or, when air drying artifact was excessive, suggested poorly preserved neutrophils or histiocytes. Five smears showed easily identified, loosely cohesive mosaic sheets of cells that resembled a HGSIL (Fig. 4). Four cases contained predominantly pseudoglandular clusters and strips of cells (Fig. 5), some of which had a “feathered” appearance suggesting endocervical adenocarcinoma or adenocarcinoma in situ.15–17 Some cases exhibited a second pattern of small, three-dimensional clusters of cells resembling endometrial glandular epithelium (Fig. 6).

The malignant cells ranged from small to large in
size and showed marked nuclear pleomorphism with scanty to moderate amounts of amphophilic cytoplasm. Many cells were binucleate or multinucleate. The nuclei were hyperchromatic, had a coarse chromatin pattern, contained indistinct nucleoli, and often showed nuclear molding. All cases showed single atypical cells with strikingly angulated hyperchromatic nuclei and nuclear smearing (Fig. 7). Mitoses were identified easily in three of the six cases, and pyknotic nuclei and nuclear debris were noted in all cases. Tumor diathesis was prominent in two cases.

**DISCUSSION**

Neuroendocrine tumors of the cervix first were described as "carcinoid tumors" by Albores-Saavedra et al. in 1976. Subsequently many different other terms have been applied, including "small cell neuroendocrine carcinoma," "small cell undifferentiated carcinoma," "small cell carcinoma," "small cell undifferentiated carcinoma," and "endocrine intermediate cell carcinoma." The diagnostic criteria for neuroendocrine carcinoma of the cervix have changed over the years. The original criteria for the diagnosis of small cell neuroendocrine carcinoma of the cervix included demonstration by histochemistry of argyrophilic granules within the cytoplasm, the presence of neuroendocrine secretory granules on electron microscopy, and demonstration of neuroendocrine differentiation by immunohistochemical methods. However, a potentially confusing observation was that some squamous carcinomas of the small cell type also could show neuroendocrine secretory granules or neu-
roendocrine differentiation by immunohistochemical methods. It was evident that endocrine carcinomas of the cervix were a heterogeneous group of tumors similar to their pulmonary counterparts. In 1996, a group of gynecologic pathologists adapted the classification system of pulmonary neuroendocrine carcinoma to the uterine cervix, classifying cervical neuroendocrine tumors into small cell carcinoma, atypical carcinoid, carcinoid, and large cell neuroendocrine carcinoma. SMCC is the most common type of neuroendocrine carcinoma of the cervix. Because neuroendocrine differentiation by immunohistochemical staining is absent in approximately 33% of the cases and because neuroendocrine secretory granules or argyrophilic staining is absent in approximately 50% of the cases, the current criteria for diagnosis mainly are based on routinely stained histologic sections.

This study confirms the low specificity of the diagnosis of SMCC when malignant cells are present on cervical smears. In this series of 13 patients, although 6 cases were diagnosed as an epithelial malignancy, none of the cases initially was diagnosed specifically on cytology as SMCC. In our six cases originally interpreted as malignant, adenocarcinomas was reported in three cases and malignant epithelial cells NOS in three cases. The smears of two of the five cytologically negative cases available for review contained a few abnormal cells (false-negative smears), reflecting an error of detection or interpretation. Other reports have noted a similar problem with cytologic diagnosis. In one case series of 14 patients, 6 patients had cervical smears taken before a histologic diagnosis and their smears all were reported as negative. In another series of 15 cases, only 1 patient’s cervical smear showed abnormal cytology. However, in these reports no mention of review of the smears is noted. As in our series, sampling error, detection error, and interpretative error most likely accounted for a proportion of the negative diagnoses. As noted, the histology of some cases showed subepithelial spread of tumor beneath an intact squamous or endocervical mucosa. It is interesting to note that one patient (Case 10) with a negative smear prior to biopsy was noted to have a malignant smear shortly after biopsy, suggesting the biopsy had exposed previously ‘hidden’ malignant cells to sampling. This subepithelial growth pattern may be a factor in the low rate of early detection of SMCC by cervical cytology.

In our series, 6 of 13 patients presented with frankly malignant smears. However, on review of available smears, two additional cases previously reported as negative were found to have abnormal cells, which although not definitely malignant would have led to a biopsy. Our findings and those in other studies suggest that SMCC often is preceded by a squamous intraepithelial lesion (squamous dysplasia), although this may not be detectable at the time of biopsy.

The cytologic features of SMCC of the cervix described briefly in three previous case reports noted that tumor cells were distributed singly or in small clusters, and were small and uniform with hyperchromatic, round nuclei showing fine chromatin and nuclear molding. One case was diagnosed correctly cytologically after confirmation by immunohistochemical stains. In contrast with these reports, the current study emphasizes the considerable cytologic and architectural pleomorphism encountered in smears of SMCC.

The current study indicates that the cytologic features of SMCC frequently are misdiagnosed as a non-small cell carcinoma. Although the cell types noted in this study resemble those of SMCC of the lung, the cell arrangements overlap with the cytologic features of small cell squamous carcinoma and adenocarcinoma, possibly reflecting the mixed exfoliative and scrape nature of the specimens and the origin from luminal and glandular surfaces.

This study of SMCC highlights a number of potential cytologic pitfalls. First, SMCC may resemble benign lesions such as “inflammatory cell exudate” or follicular cervicitis. Air drying artifact may result in cells being interpreted as histiocytes or degenerate neutrophils. Careful high-power examination of inflammatory aggregates for atypical mononuclear cells is necessary to avoid this error. In addition, the absence of tingible body macrophages should make suspect a diagnosis of follicular cervicitis. Second, if ball-like clusters of small cells are present and the smear is taken within 10 days of the previous menstrual cycle, cells of SMCC could be mistaken for normal endometrial cells. Furthermore, SMCC with degenerate or air-dried intermediate cells may resemble endometrial stromal cells. Careful high-power examination should reveal the nuclear pleomorphism and dense chromatin of SMCC and may reveal mitotic figures and nuclear debris.

In the current study, two of six malignant cytologic diagnoses initially were classified as endocervical adenocarcinoma. Tumor cells with a small to moderate amount of cytoplasm and fusiform nuclei arranged in gland-like rosettes and showing nuclear palisading mimicked endocervical adenocarcinoma. In retrospect, the lack of true gland formation, the coarse texture of nuclear chromatin, nuclear smearing, apoptotic bodies, and nuclear molding are unusual for adenocarcinoma.

SMCCs can be difficult to differentiate from the
small cell variant of squamous cell carcinoma both on histology\textsuperscript{7} and on cytology. Although not encountered in our series, the mosaic pattern of intermediate cells could be interpreted as squamous cell carcinoma of the small cell type. On cervical smears, small cell squamous cell carcinomas show slightly more cytoplasm, well defined cytoplasmic borders, and less nuclear molding and smearing effect. In addition, the background of smears of squamous cell carcinoma usually contains cells consistent with a squamous intraepithelial lesion.

In addition to the small cell variants of squamous cell carcinoma and adenocarcinoma, malignant lesions with small cell morphology include malignant lymphoma, metastatic carcinoma, large cell neuroendocrine carcinoma, and malignant melanoma (Fig. 8). Careful examination for the nuclear and cytoplasmic features of these lesions as well as a supportive history may be helpful. Distinction of SMCC from lymphoma on smears may not be possible. In contrast to lymphoma, SMCCs tend to have at least some cohesive groups of cells in the smear. Identifying the nuclear features of lymphoma such as prominent nucleoli\textsuperscript{22} or nuclear clefts\textsuperscript{23} may be helpful. A panel of ancillary immunohistochemical stains for leukocyte common antigen, cytokeratin, chromogranin, and neuron specific enolase also might be helpful, as demonstrated in previous reports,\textsuperscript{11,19,22–24} but is of little practical value in screening cytology. Suspicion of any malignant diagnosis should prompt biopsy.

Early diagnosis of SMCC is important. SMCCs have a rapid clinical course and an aggressive behavior.\textsuperscript{2–8} Earlier reports indicated the majority of patients died of disease within 3 years\textsuperscript{3–6,8} with a 5-year survival rate in 1 study of 14%.\textsuperscript{8} Experience at the British Columbia Cancer Agency with SMCC has led to an aggressive treatment protocol of combination chemotherapy with cisplatin and etoposide, regional external beam radiation, brachytherapy (intracavity cesium insertion), and prophylactic brain radiation. Selected patients have undergone abdominal hysterectomy in lieu of brachytherapy. This treatment protocol has resulted in a 5-year survival rate of close to 50%.\textsuperscript{25}

Cervical smears of SMCC of the cervix have several cell variants and cytologic patterns. Although

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\caption{Cervical smears of mimics of small cell carcinoma of the cervix (SMCC). Separation of SMCC cytologically from other malignant lesions may not be possible. (a) Large cell neuroendocrine carcinoma. (b) Squamous cell carcinoma in situ. (c) Adenocarcinoma in situ. (d) Metastatic lobular carcinoma of the breast.}
\end{figure}
many cytologic features are similar to those of SMCC of the lung, a specific diagnosis of SMCC on cervical smears is difficult. The current study suggests that the cervical smear is not specific and is relatively insensitive to the diagnosis of SMCC. The morphologic features may simulate several benign and other malignant lesions. Attention to cell patterns, the nuclear features, nuclear molding, and unusually high mitotic rate, and single cell necrosis may suggest the correct diagnosis. Because SMCC is a very aggressive malignancy, suspicion of the diagnosis should prompt urgent biopsy and treatment.

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