Combined Large Cell Neuroendocrine Carcinoma and Papillary Serous Carcinoma of the Endometrium With Pagetoid Spread

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- Neuroendocrine carcinomas of the endometrium are rare tumors that can be pure, combined with endometrioid adenocarcinoma, or a component of malignant mixed müllerian tumor. Recently, a case of combined small cell carcinoma and papillary serous carcinoma of the endometrium was described for the first time. We report the first case, to our knowledge, of combined large cell neuroendocrine carcinoma and papillary serous carcinoma of the endometrium, with an unusual pagetoid spread of the neuroendocrine component into normal endometrial and endocervical glands. The endometrial carcinoma had a small serous component, but most of the tumor was characterized by solid sheets of medium to large cells with abundant mitotic figures, numerous apoptotic bodies, and foci of necrosis. This component was diffusely positive for neuroendocrine markers. Following surgery, the patient was treated with radiation therapy and chemotherapy. She was without evidence of progression at 5 months of follow-up.

Arch Pathol Lab Med. 2008;132:1821–1824

Although mixed endometrial carcinomas with a neuroendocrine component are rare;\(^2\) combined neuroendocrine carcinoma and papillary serous carcinoma of the endometrium is even more unusual.\(^3\) We report the first case, to our knowledge, of a mixed large cell neuroendocrine carcinoma and papillary serous carcinoma of the endometrium, which had pagetoid spread of the neuroendocrine component into normal endometrial and endocervical glands. The morphologic pattern and immunohistochemical findings support a diagnosis of a primary endometrial tumor with divergent differentiation.

REPORT OF A CASE

Clinical History

The patient was a 59-year-old woman (gravida 2, para 2), with a medical history significant for breast cancer diagnosed 8 years before presentation. She had been treated with a lumpectomy and axillary lymph node dissection, radiation, and chemotherapy. She had taken tamoxifen for 5 years, and her follow-up mammograms and breast ultrasound study results were normal. The breast specimen and pathology report were not available for our review.

The patient had a routine Papanicolaou test, which contained cells interpreted as atypical glandular cells of undetermined significance. This was followed by a loop electrocautery conization and dilation and curettage, which established a diagnosis of mixed serous and poorly differentiated carcinoma. A 1-cm nodule was found in the left vaginal wall on examination. A biopsy of this nodule was diagnosed as metastatic high-grade neuroendocrine carcinoma. A modified radical hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and pelvic-aortic lymph node dissection was then performed. The vaginal lesion was incompletely excised because it extended into underlying soft tissue.

The uterus contained high-grade endometrial carcinoma, predominantly neuroendocrine carcinoma, with a serous component. The fallopian tubes, ovaries, omentum, and lymph nodes were negative for tumor. A pelvic washing performed during surgery was negative for malignant cells. The tumor stage was FIGO (International Federation of Gynecologists and Obstetricians) IIIB.

The residual vaginal lesion was treated with whole-pelvic radiation therapy and brachytherapy. The patient is currently receiving chemotherapy and was without evidence of progression at her 5-month follow-up visit.

MATERIALS AND METHODS

Immunohistochemical studies were performed using the avidin-biotin-peroxidase method, with antisera to p53, p16, neuron-specific enolase, CD57, synaptophysin, chromogranin, and CD56. Antibody information and the immunohistochemical profiles of the neuroendocrine and papillary serous components are summarized in the Table.

PATHOLOGIC FINDINGS

The radical hysterectomy specimen consisted of a 2.02 kg uterus (12.5 × 7.2 × 5.0 cm) with attached unremarkable adnexae. The cervix was stenotic, with the ectocervix covered by tan, irregular mucosa. The endometrial lining was white-tan and diffusely friable; an area suggestive of myometrial invasion was seen. The fallopian tubes and ovaries were unremarkable.

On microscopic examination, most of the endometrial tumor was characterized by solid sheets of medium to large polygonal cells with scant to moderate amphophilic cytoplasm, foci with cords and trabeculae (Figure, A inset), and focal pseudosertiform formation. There were abun-
Summary of Immunohistochemical Staining*

<table>
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<tr>
<th>Marker</th>
<th>Clone</th>
<th>Dilution</th>
<th>Source</th>
<th>Treatment</th>
<th>Neuroendocrine Component; Serous Component†</th>
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<td>DO-7</td>
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<td>1:25</td>
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<td>NSE</td>
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<td>Predilute</td>
<td>Dako, Carpinteria</td>
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<td>CD57</td>
<td>HNK-1</td>
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<td>Tris</td>
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<td>Citrate</td>
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<td>1:50</td>
<td>Zymed Laboratories, Inc, South San Francisco, Calif</td>
<td>Citrate</td>
<td>F; N</td>
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</tbody>
</table>

* NSE indicates neuron-specific enolase; Tris, tris(hydroxymethyl)aminomethane; synapto, synaptophysin; and chromo, chromogranin.
† Distribution of staining: F indicates focal (<50%); D, diffuse (>50%); and N, negative.

A. Large cell neuroendocrine carcinoma. Note the frequent apoptotic bodies and papillary serous carcinoma component bordering the lumen and (inset) tumor with irregular islands and trabeculae (hematoxylin-eosin, original magnifications ×200). B. Combined papillary serous carcinoma and large cell neuroendocrine carcinoma. Note neuroendocrine component on the left and (inset) papillary serous carcinoma component (hematoxylin-eosin, original magnifications ×100 and ×200 [inset]). C. Endocervical gland with pagetoid spread of neuroendocrine cells (hematoxylin-eosin, original magnifications ×100 and ×400 [inset]). D. Synaptophysin staining in the neuroendocrine component and (inset) endocervical gland with pagetoid spread of neuroendocrine cells with strong staining for synaptophysin (immunoperoxidase stain, original magnifications ×400).

dant mitotic figures (up to 19 mitoses per 10 high-power fields), numerous apoptotic bodies (Figure, A), and foci of geographic necrosis. Nuclear molding and crush artifact were focally present, and some of the large cells were multinucleated. A small area of papillary serous carcinoma was present (Figure, A, B, and B inset). The serous carcinoma was surrounded by the poorly differentiated component, but a definitive transition between the elements was not seen (Figure, A and B). The poorly differentiated component also surrounded benign endometrial glands. Within some benign endometrial and endocervical glands, pagetoid spread of the poorly differentiated cells was
identified (Figure, C, C inset, and D inset). This pagetoid involvement was characterized by tumor cells located bet-
 tween the normal endocervical or endometrial epithelium and the basement membrane. Involved endocervical glands were found up to 3 mm away from the main tumor. The poorly differentiated component invaded 0.9 cm into a 2.1-cm-thick myometrium; there was extensive lymph vascular-space invasion and focal involvement of the cer-
 vical stroma. No heterologous or sarcomatous components were identified.

The poorly differentiated carcinoma component was present in the vaginal specimens. The adenexae, omentum, and right and left pelvic and paraaortic lymph nodes were free of tumor.

The immunohistochemical results are summarized in the Table. The poorly differentiated component was diffusely positive for synaptophysin (Figure, D), with scattered staining for CD56, CD57, and neuron-specific enolase; chromogranin was negative. This immunohistochemi-
cal staining pattern, together with the histologic features, was diagnostic of large cell neuroendocrine carcinoma. The neuroendocrine carcinoma cells with pagetoid in-
 volvement of the endocervical glands were also positive for synaptophysin (Figure, D inset). The serous compo-
nent was negative for the neuroendocrine markers, where-
as p53 was overexpressed.

**COMMENT**

Neuroendocrine carcinomas of the endometrium are ag-
 gressive tumors, usually presenting in perimenopausal or
 postmenopausal women with a mean age of 60 years, 1
decade later than endometrioid carcinomas.4 Abnormal uterine bleeding is the most frequent initial complaint.1,2

Neuroendocrine carcinomas are often polypoid bulky
tumors that are deeply invasive. Histologically, they can
be pure small cell carcinoma or large cell carcinoma, ad-
mixed with endometrioid adenocarcinoma, or a compo-
nent of a malignant mixed müllerian tumor.1,2 The inva-
sive component is generally the neuroendocrine carcinoma, but intermixed neuroendocrine and nonneuroendocrine components can also be present.1 The presence of neuro-
endocrine features in an endometrial carcinoma appears to be associated with an increased frequency of deep myo-
 metrial invasion, metastasis to distant organs, and de-
 creased survival.5 Although both neuroendocrine and glandular components can be found in metastases, meta-
tasis of the neuroendocrine component alone appears to be most common.3

Large cell neuroendocrine carcinomas have been pre-
viously described in the cervix and ovary and, morpho-
 logically, resemble large cell neuroendocrine carcinomas in other organs. They are characterized by large polygonal tumor cells, with organoid, trabecular, or cordlike growth patterns. Peripheral palisading, necrosis, vesicular nuclei, and frequent mitotic figures and apoptotic bodies are characteristic.6 The diagnosis is confirmed by immunohistochemical staining for neuroendocrine markers.

There are only 2 previous reports, to our knowledge, of combined neuroendocrine carcinoma and papillary serous carcinoma: one3 described a composite papillary serous carcinoma and small cell carcinoma of the endometrium, and the other7 described a collision tumor with serous car-
 cinoma and carcinoid tumor involving the mesentery. The endometrial tumor, in a 79-year-old woman with post-
 menopausal bleeding, was composed of several small pol-
ypoid lesions. Histologically, papillary serous carcinoma and small cell neuroendocrine carcinoma components were present. The serous component was present at the endometrial surface and deeply invaded the myometrium; the small cell component was only identified in the inva-
sive tumor.3

The second tumor, in a 70-year-old woman with a his-
tory of colonic mucinous carcinoma, consisted of several nodules in the mesentery of the distal ileum.7 On micro-
scopic examination, the nodules were found to be com-
posed of an admixture of carcinoid tumor and serous car-
cinoma. This was interpreted as a collision tumor after the serous carcinoma and the neuroendocrine carcinoma showed loss of heterozygosity on chromosomes 4q and 17 but involvement of different alleles at the same locus.7

Although controversial, it appears that there is an as-
 sociation between tamoxifen therapy and high-grade and
 advanced-stage endometrial tumors. Compared with spo-
radic tumors, there is an increased risk of poorly differ-
 entiated, nonendometrioid carcinomas and malignant mixed müllerian tumors.3 This association appears to be time and dose dependent, and the risk of developing en-
dometrial tumors remains even after discontinuation of
tamoxifen. In patients who have had tamoxifen treatment, the median time to diagnosis of endometrial tumors is 40 months after the breast carcinoma diagnosis.8

In the only previously reported case of primary carci-
noid tumor of the uterine corpus in a patient receiving
tamoxifen therapy for breast cancer, the duration of treat-
ment was not mentioned. Most likely, there is no causal relationship between tamoxifen therapy and uterine neu-
roendocrine carcinomas, but given the rarity of uterine neu-
roendocrine tumors and the reported concomitant ex-
posure to tamoxifen in 2 cases, including our case, an as-
sociation is difficult to rule out.9

To our knowledge, the current case is the first reported combined endometrial large cell neuroendocrine carcino-
 ma and papillary serous carcinoma. Although the carci-
noma in this case could be a collision tumor, it seems most
likely to be a combined carcinoma with 2 distinct lines of differentiation because the 2 components were intimately admixed, both were positive for p53 and p16, and no other primary tumor was identified. The neuroendocrine and serous components may both have arisen from pluripo-
tential cells that differentiated along 2 distinct paths, or
the neuroendocrine carcinoma could have arisen second-
arily from the serous cells. Given that combined serous and neuroendocrine carcinomas are rare and that mülle-
rian tumors with divergent differentiation are compara-
tively common, the former seems more likely.

Epithelial pagetoid extension of neuroendocrine carcino-
 noma has been recognized in tumors involving the anal
canal and urethral mucosa and in Merkel cell carcinomas of the skin.10-12 but, to our knowledge, epithelial pagetoid extension has not been reported previously in neuroen-
docrine tumors of the endometrium or cervix. In this case, pagetoid spread was identified in benign endometrial glands and in endocervical glands located at least 3 mm from the main tumor. This phenomenon is of interest be-
cause it could potentially lead to incomplete resection of a tumor. Neuroendocrine carcinoma did involve the vag-
inal apex in this case, although we did not identify pag-
etoid extension in the ectocervical sections examined. High-grade neuroendocrine carcinoma with pagetoid spread should also be included in the differential diag-

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**Arch Pathol Lab Med—Vol 132, November 2008**

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nosis of cervical melanomas because it could mimic melanoma with an in situ component.

In summary, we have reported a case of combined large cell neuroendocrine carcinoma and serous carcinoma of the endometrium, with pagetoid extension of the neuroendocrine component into benign endometrial and endocervical glands. This case further expands the known range of endometrial neuroendocrine carcinomas.

References