Primary Vaginal Mucinous Adenocarcinoma of Intestinal Type, Associated With Intestinal Metaplasia of Skene Ducts in a Diethylstilbestrol-Exposed Woman

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ABSTRACT

Objectives: Primary mucinous vaginal adenocarcinoma of intestinal type is an extremely rare malignancy of uncertain histogenesis, which makes for a diagnostic challenge. We report a case and describe the histopathologic features and the unusual immunoprofile of this rare entity.

Methods: We report a case of vaginal mucinous adenocarcinoma of intestinal type in a diethylstilbestrol-exposed woman in which intestinal metaplasia of the Skene duct was found at the time of recurrence.

Results: As the histogenesis of primary vaginal intestinal-type adenocarcinomas remains uncertain, the finding of Skene duct metaplasia in association with invasive adenocarcinoma lends support to the origin of vaginal mucinous adenocarcinomas of intestinal type to be metaplasia, at least in some cases. Such an origin accounts for the unusual immunohistochemical profile, which raises concern for a metastatic adenocarcinoma of gastrointestinal origin.

Conclusions: Recognition of this rare entity is important, particularly to avoid the pitfall of misdiagnosing metastatic disease.

Primary vaginal adenocarcinoma is a rare entity, comprising only 1% to 2% of all gynecologic malignancies. 1 Most vaginal tumors are squamous cell carcinomas, with adenocarcinomas accounting for only 5% to 15% of malignancies. Vaginal adenocarcinoma, most frequently, is metastatic from another site or, less commonly, with clear cell histology occurring in young women previously exposed to diethylstilbestrol (DES) in utero. Primary mucinous vaginal adenocarcinomas have been described in DES-exposed women, but this entity remains very rare.

Rarer than primary vaginal adenocarcinomas are those of the female urethra, accounting for 0.003% of malignancies in the female genitourinary tract. 2, 3 Located at the distal female urethra, anterior to the vaginal wall, are two small structures called Skene glands. Skene glands have historically been considered the homolog of the prostate, having similar structural components and function, even producing prostate-specific antigen (PSA). 3, 4 Urethral adenocarcinomas in women have historically been assumed to have arisen from Skene glands. However, PSA negativity on many primary urethral carcinomas suggests that adenocarcinomas arising directly from Skene glands (prostate homolog) compose, in fact, the minority of cases. 3 Suggested possible etiologies of these rare carcinomas include metaplastic urothelium, tissues of Müllerian origin, and intestinal metaplasia. 3- 5

We present a case of a primary mucinous vaginal adenocarcinoma associated with intestinal metaplasia of the Skene glands and the immunohistochemical profile of this rare tumor.
The patient is a 64-year-old postmenopausal, asymptomatic woman whose medical history is notable for in utero DES exposure and a remote history of low-grade vulvar dysplasia (vulvar intraepithelial neoplasm I) treated with simple vulvectomy 20 years prior to presentation. On a routine health examination, the patient was found to have a 2-cm, ulcerated, peduncular, nontender nodule on the posterior vaginal wall, approximately 1 cm from the introitus. The nodule involved the full thickness of the vaginal wall. The anterior rectal mucosa was visibly intact and, on digital rectal examination, uninvolved by tumor. Rectovaginal examination demonstrated no proximal or lateral thickening of the paravaginal space.

The nodule was biopsied, and a diagnosis of mucinous adenocarcinoma was rendered. An extensive panel of immunohistochemical stains suggested the diagnosis of metastatic adenocarcinoma. Based on the immunoreactivity profile, a metastatic neoplasm of gastrointestinal origin was suggested. Extensive clinical and radiologic investigations, including a Papanicolaou test, endometrial biopsy, mammogram, chest radiograph, positron emission tomography–computed tomography, rectal ultrasound, colonoscopy, and upper endoscopy, failed to identify a primary site. After correlation with the radiographic and clinical findings, the diagnosis of primary vaginal mucinous adenocarcinoma of intestinal type was reported. The patient underwent a posterior partial distal vaginectomy, followed by adjuvant external beam radiation. She responded well to treatment and entered surveillance.

Twenty-two months following surgery, a 1-cm fungating mass was identified protruding through the urethral meatus. The patient denied dysuria or bleeding. The mass was biopsied, revealing mucinous adenocarcinoma with similar morphologic features as that seen in the vaginectomy specimen. She

**Table 1**

Results of Immunohistochemical Profile

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clone</th>
<th>Result in Tumor Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK7</td>
<td>OV-TL 12/30 (Thermo Scientific, Rockford, IL)</td>
<td>Focally positive</td>
</tr>
<tr>
<td>CK20</td>
<td>Ks20.8 (Thermo Scientific)</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>CDX-2</td>
<td>CDX2-88 (Biogenex, Fremont, CA)</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>ER</td>
<td>SP1 (Thermo Scientific)</td>
<td>Negative</td>
</tr>
<tr>
<td>TTF-1</td>
<td>SPT24 (Vision Biosystem, Newcastle, England)</td>
<td>Focally positive</td>
</tr>
<tr>
<td>PAX-2</td>
<td>Polyclonal (Invitrogen, Camarillo, CA)</td>
<td>Negative</td>
</tr>
<tr>
<td>PAX-8</td>
<td>MRQ-50 (Ventana, Rocklin, CA)</td>
<td>Negative</td>
</tr>
<tr>
<td>p53</td>
<td>Rabbit monoclonal, clone SP5 (Thermo Scientific)</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>Ki-67</td>
<td>Rabbit monoclonal, clone SP6 (Thermo Scientific)</td>
<td>&gt;75% positive</td>
</tr>
<tr>
<td>p16</td>
<td>E6H4TM (MTM Labs, Tucson, AZ)</td>
<td>Focally positive</td>
</tr>
<tr>
<td>PSA</td>
<td>Polyclonal (DAKO, Carpinteria, CA)</td>
<td>Negative</td>
</tr>
</tbody>
</table>

CDX-2, caudal-type homeobox transcription factor 2; CK7, cytokeratin 7; CK20, cytokeratin 20; ER, estrogen receptor; PAX-2, paired box protein 2; PAX-8, paired box protein 8; TTF-1, thyroid transcription factor.
underwent a cystoscopy, which showed the lesion to involve approximately one-third of the distal urethra. The proximal half of the urethra, bladder, and trigone was normal. A subsequent distal urethrectomy and partial vaginectomy were performed, with negative margins.

Pathologic Findings

The partial vaginectomy specimen from the initial resection measured 3.6 × 2.5 cm, with a depth of 2.0 cm. A 0.7 × 0.5-cm hyperemic, ulcerated lesion overlying a firm nodule was identified, which featured a firm, multinodular, centrally mucinous cut surface. Microscopic examination revealed a 1.6 × 1.0-cm mucinous adenocarcinoma focally ulcerating through the overlying vaginal mucosa. The tumor was characterized by complex glands with cribriform growth pattern in the background of abundant extracellular mucin. The malignant glands were lined by stratified columnar cells with a moderate amount of eosinophilic cytoplasm, conspicuous intracellular mucin, and large, irregular nuclei with prominent nucleoli. An Alcian blue/periodic acid–Schiff stain showed cytoplasmic as well as abundant extracellular neutral mucin. The specimen was analyzed for high-risk human papillomavirus DNA by in situ hybridization and polymerase chain reaction, the results of which were negative.

Immunohistochemical stains included cytokeratins 7 and 20, caudal-type homeobox transcription factor 2, estrogen receptor, thyroid transcription factor, p16, paired box proteins 2 and 8, p53, PSA, and proliferation marker Ki-67 (Table 1).
The distal urethrectomy and partial vaginectomy specimen from the second surgery measured 3.5 × 1.2 cm, with a depth of 0.6 cm. A 1.1 × 1.1 × 0.4-cm firm, tan-white fungating lesion was identified with a 0.1-cm depth of invasion. Microscopic examination revealed a mucinous adenocarcinoma with similar morphology as the previous specimen, involving the surface of the urethral urothelial/transitional epithelium at the junction of the transitional to squamous epithelium with focal extension into the underlying stroma. Intestinal metaplasia of Skene ducts was present. The morphologic similarity to the prior tumor suggested recurrence; however, a new primary could not be entirely excluded.

Discussion

Primary vaginal carcinomas are uncommon, with squamous cell carcinoma being the most prevalent histology. Most adenocarcinomas of the vagina are metastatic from other sites, such as colon, uterus, or breast, and must be excluded. Most vaginal adenocarcinomas are of clear cell histology related to in utero exposure to DES, although this is becoming increasingly uncommon. The glands of preexisting vaginal adenosis are considered an origin for clear cell adenocarcinomas.

Primary vaginal adenocarcinoma can be divided into different subtypes, including clear cell, endometrioid, serous, and mucinous carcinomas. Mucinous adenocarcinomas of the vagina are rare and can be further subtyped into endocervical and intestinal types.

The histogenesis of mucinous adenocarcinoma of the vagina remains the subject of speculation. Endocervical-type mucinous adenocarcinomas have been proposed to arise from vaginal adenosis and/or endocervicosis. Intestinal types have been reported arising from vaginal tubular or villous adenomas and adenosis. Dysplastic enteric epithelium secondary to surgical manipulation has also been described as a possible origin of mucinous vaginal tumors. Other suggested histogeneses of intestinal-type vaginal adenocarcinomas include cloacal and mesonephric remnants, gastrointestinal metaplasias and heterotopias, endometriosis, and urethral origin.

Primary urethral carcinoma is rare, with only 540 cases in women identified between 1973 and 2002. Similar to vaginal carcinomas, most urethral malignancies are squamous cell carcinomas (70%), followed by transitional cell carcinomas (20%), with adenocarcinomas (8%-10%) making up the minority of cases. Morphologic and immunohistochemical studies have further subdivided urethral adenocarcinomas into mucinous, clear cell, and cribriform types, of which the mucinous subtype predominates. Mucinous adenocarcinoma of the female urethra, composed of enteric-type epithelium with abundant mucus, resembles colorectal carcinoma, whereas the clear cell and cribriform subtypes resemble clear cell carcinomas of Müllerian origin and adenocarcinomas of the prostate, respectively.
urethral adenocarcinomas to be negative for PSA, suggesting heterogeneous phenotypes and histogenesis from urethelial metaplasia and intestinal metaplasia, in addition to PSA-negative cells of Skene glands.\textsuperscript{2,3,5,20}

Vaginal adenocarcinoma associated with DES exposure in utero is most often of clear cell–type histology. To our knowledge, our case represents the first reported case of intestinal-type vaginal adenocarcinoma arising in a DES-exposed woman. Unfortunately, the recent review of 14 patients with intestinal-type vaginal lesions did not provide clinical data as to DES exposure history.\textsuperscript{21}

Our case is similar morphologically to a vaginal intestinal-type adenocarcinoma reported by Ditto et al.,\textsuperscript{7} although in their case, the tumor arose in a patient not exposed to DES. Unlike their patient, who was treated with surgical resection followed by chemoradiation and remained disease free (at 32 months), our patient underwent surgical resection followed by external beam radiation only. Her carcinoma subsequently recurred 22 months later, and she underwent a second surgical procedure. She is now disease free with a follow-up time of 11 months, at the time of this manuscript submission.

The finding of intestinal metaplasia involving the Skene gland supports a hypothesis that the histogenesis of intestinal-type vaginal tumors may be related to intestinal metaplasia. No metaplasia was identified in the original resection, perhaps due to the malignancy obliterating a preexisting metaplastic focus. Intestinal metaplasia, although rare, has been found near the urethral meatus of females ranging from 2 to 78 years of age. In younger individuals, the metaplasia is often associated with developmental malformations, while in adults and older women, it is felt to likely be a metaplastic response to chronic injury or obstruction.\textsuperscript{22} In addition, our case raises the possibility of a relationship between in utero DES exposure and intestinal metaplasia of the Skene gland that, to our knowledge, has never been reported.

Intestinal-type adenocarcinoma of the vagina will continue to be a challenge for the surgical pathologist since the morphology as well as the immunohistochemical profile of the tumor so closely mimics that of a gastrointestinal malignancy. Indeed, immunohistochemistry is of no value in excluding a colorectal metastasis,\textsuperscript{21} and a full clinicoradiologic workup of the patient is mandated prior to making this rare diagnosis.

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References


