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Papillary squamous cell carcinoma

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This regular feature presents special issues in oncologic pathology.

Introduction

Primary malignant tumors of the vagina are rare, representing only 1% to 2% of all malignancies of the female genital tract. Of these, squamous cell carcinoma (SCC) is the most prevalent neoplasm, accounting for over 90% of vaginal tumors. While papillary squamous cell carcinoma (PSCC) of the uterine cervix has been previously reported, a papillary variant of primary vaginal SCC has not been described, to our knowledge, in the medical literature.

PSCC of the vagina should be differentiated from other benign and malignant papillary tumors of the vagina including fibroepithelial polyps, squamous papilloma, condyloma accuminatum, transitional carcinoma, transitional carcinoma with squamous differentiation, verrucous carcinoma, and botryoid rhabdomyosarcoma. The prognosis of the cervical counterpart of PSCC is similar to that of invasive SCC except for the high incidence of late recurrences in PSCC.

Case Report

A 49-year-old woman (para 4-0-2-2) presented with a complaint of postmenopausal vaginal bleeding. Clinical examination revealed two vaginal polypoid lesions, 1.2 cm and 0.6 cm in largest diameter, located on the posterior and right vaginal wall, respectively. Both vaginal polyps were excised. Postoperative radioactive implant therapy was administered (two implants for a total of 62.83 Gy). The patient is doing well and is free of disease at the time of this report. A review of her medical records revealed a past history of cervical intraepithelial neoplasia for which she underwent hysterectomy in 1971. No invasive carcinoma was found in the hysterectomy specimen. Also, a previous vaginal lesion was diagnosed as "Bowen's disease" and treated with laser surgery in 1990. This lesion was not available for review.

Methods

Biopsy tissue sections were cut from 10% buffered formalin paraffin blocks. Serial 5-µm-thick sections were mounted on glass slides and stained with hematoxylin and eosin, as well as the following undiluted...
monoclonal antibodies: AE1/ AE3 Pan-Cyto keratin (Signet Laboratory, Dedham, Mass), cytokeratin 7 and 20 (DAKO, Carpinteria, Calif), chromogranin (Immunon, Detroit, Mich), neuron-specific enolase (DAKO, Carpinteria, Calif), and synaptophysin (Biogenex, San Ramon, Calif). Sections were also stained with undiluted polyclonal antibody to human papilloma virus (Biogenex, San Ramon, Calif). The immunohistochemical stains were performed using the avidin biotin peroxidase complex technique (ABC Kit, Vector Laboratories, Burlingame, Calif). Sections of pancreatic tissue and papilloma virus infected tissue were used as positive controls in each case. Controls for specificity included the incubation of the tissue sections with unrelated primary mouse monoclonal antibodies, unrelated secondary antimouse monoclonal antibody, and phosphate buffered saline. Samples from the paraffin block were used for electron microscopy. Tumor tissue was deparaffinized in xylene, rehydrated, and incubated over-night at 40?C in 2.5% glutaraldehyde. Following washing in 0.1M phosphate buffer, fixation in 1% osmium tetroxide for one hour at 4?C, and dehydration, the tissue was embedded in LX112 epoxy resin (Ladd Corp, Burlington, Vt). Thin sections were cut and stained for 10 minutes in 8% aqueous uranyl acetate and 5 minutes in Reynold’s lead citrate. Sections were examined with a Philips CM10 transmission electron microscope.

Results

**Gross:** The biopsy specimens were tan-white polypoid lesions measuring 1.5 cm and 1.1 cm in greatest dimension, respectively.

**Histopathology:** The low-power microscopic examination revealed stratified squamous mucosa with a papillary neoplasm (Fig 1).
The papillae were covered by several layers of basaloid cells with scant cytoplasm and hyperchromatic nuclei (Fig 2).
There were numerous mitoses and no maturation. Single-cell keratinization was noted focally (Fig 3).

An invasive component was easily identified at the base of this papillary tumor. The invasive area was characterized by nonpapillary, non-keratinizing SCC growing in nests with vague peripheral palisading. The invasive tumor was surrounded by a stromal desmoplastic reaction (Fig 4).
Neither viral changes nor Bowen’s disease was identified.

Immunohistochemistry: Immunostains for chromogranin, neuron-specific enolase, synaptophysin, and human papilloma virus were negative. The tumor cells were pancytokeratin (AE1/AE3)-positive but cytokeratin 20-negative (Fig 5A). Only focal areas of cytokeratin 7 immunoreactivity were identified (Fig 5B), away from the papillary component of the tumor. Positive and negative controls were appropriate.
Ultrastructural Features: The tumor cells were polygonal, with an increased nuclear-to-cytoplasmic ratio, and contained numerous desmosomes and cytoplasmic tonofilaments. Neither neurosecretory granules nor secretory granules were identified. Viral particles were not present.

Discussion

In 1986, Randall et al. described an unusual variant of SCC of the uterine cervix that was designated PSCC. PSCC is characterized by multiple papillary projections lined by dysplastic cells. PSCC may consist of an in situ component alone, or it may demonstrate invasion. Deep biopsies are therefore crucial to rule out invasive tumor.

Vaginal PSCC, however, has not been previously reported. Fetissof et al. described four papillary vaginal tumors in a 76-year-old woman with a previous history of transitional cell carcinoma of the renal pelvis. The authors interpreted the vaginal lesions as primary papillary carcinomas resembling transitional cell carcinoma. The tumor reported here exhibits papillae lined by several layers of "basaloid-like" cells, with minimal maturation and rare squamous differentiation, together with areas of invasive SCC. These histological characteristics, along with the absence of immunohistochemical and ultrastructural evidence of neuroendocrine, transitional, and/or glandular differentiation, suggest that this tumor represents a unique occurrence of primary PSCC in the vagina.
In order to substantiate a claim of primary carcinoma of the vagina, local extension and metastatic disease must first be ruled out.\textsuperscript{5,6} Our patient underwent a hysterectomy 25 years prior to the identification of the vaginal lesions, making metastatic disease from an undocumented cervical PSCC highly unlikely. In addition, the location of the polyoid growth observed grossly in our patient occurred within 3 cm of the introitus, well away from the historical surgical margin. Lastly, the metastatic disease workup in our patient consisted of colonoscopy, cystoscopy, abdominal and pelvic computed tomography, and hepatic ultrasound, all of which were negative. Given these facts and the accepted criteria that a patient must be free of vulvar and cervical cancer at the time of diagnosis and for a period of 10 years prior to diagnosis,\textsuperscript{6} it is reasonable to conclude that our patient developed a primary vaginal PSCC.

Although this primary vaginal tumor was histologically identical to that described in cervical PSCC, careful consideration was given to other lesions in the differential diagnosis. Benign lesions such as transitional cell metaplasia were ruled out by the histological evidence of invasion. Multiple patterns of malignancy have been noted in the vagina. The majority of primary vaginal carcinomas (>90%) are SCCs.\textsuperscript{2} They are usually well differentiated and do not demonstrate papillary projections or basaloid features.

A less common variant of SCC of the vagina is verrucous SCC, estimated to represent 1% of all vaginal carcinomas.\textsuperscript{1} Grossly, this tumor is exophytic, fungating, and sometimes ulcerated, with extension over a large area. Microscopically, the tumor has bland cytologic features and pushing margins. Warty (condylomatous) carcinoma of the vagina also shows exophytic papillary architecture, with the addition of prominent koilocytotic atypia not usually seen in PSCC.

An exceedingly rare variant of SCC, with features similar to basal cell tumors of the skin, is the basaloid variant.\textsuperscript{7} Papillary architecture, however, has not been described in this entity. Adenosquamous carcinoma of the vagina usually exhibits a mixture of squamous and glandular differentiation without papillary projections.\textsuperscript{8,9} Papillary projections would also be "unusual" in entities such as malignant melanoma, lymphoma, neuroendocrine tumors and sarcoma, except for a botryoid rhabdomyosarcoma. The latter entity usually occurs in young patients and is histologically incompatible with the lesion described here. Immunohistochemical and ultrastructural findings eliminate these diagnostic considerations.

The possibility of a transitional cell carcinoma with focal squamous cell differentiation must be considered. The difference between this tumor and PSCC can be very subtle; in fact, some of the cases reported by Randall et al\textsuperscript{8} as PSCC are now believed to be examples of transitional cell carcinoma. However, when examined at high power, this vaginal carcinoma revealed squamous appearance and single-cell keratinization. Furthermore, this tumor was negative when stained with cytokeratin 20 and only focally and weakly positive for cytokeratin 7. Both of these markers are usually strongly positive in transitional cell carcinoma.\textsuperscript{10-12} Cytokeratin 20 is also invariably negative in SCCs.\textsuperscript{12}
The history of both cervical and vaginal intraepithelial neoplasms in our patient suggests a possible oncogenic human papilloma virus infection of the lower genital tract. The histologic, immunohistochemical, and ultrastructural features of this vaginal papillary lesion, however, lack evidence of a viral infection.

Clinically, our patient presented with vaginal bleeding, as did the majority of patients described by Randall et al.\textsuperscript{3} Of their nine patients, three developed recurrent disease: one patient died of disseminated disease, and another died of concurrent duodenal adenocarcinoma. Despite these historical observations, generalization about prognosis and tumor behavior at the vaginal site will require the evaluation of additional cases. At the last follow-up in July of 1997, our patient was still free of disease.

References


