Vulvar Adenocarcinoma with Neuroendocrine Differentiation: A Case Report

Vulvar Adenocarcinoma with Neuroendocrine Differentiation: A Case Report

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Precis:

Vulvar adenocarcinomas are uncommon. An exceptionally rare adenocarcinoma with neuroendocrine differentiation is presented.

Key words: vulvar neoplasms, adenocarcinoma, neuroendocrine differentiation

Introduction:

Vulvar cancer makes up 3-5% of all female genital tract cancers. Of those, the majority are squamous cell carcinomas. Primary vulvar adenocarcinomas make up 1% of all vulvar cancers and may arise from skin adnexal structures, anogenital mammary-like glands, vestibular glands or Bartholin glands.[1] Vulvar adenocarcinomas are categorized into three subtypes: sweat gland carcinomas, primary "mammary-like" adenocarcinomas and extra-mammary Paget's disease (EMPD).[2] However, the true histologic origins of these tumors are poorly understood. EMPD is thought to be derived from eccrine, apocrine and mammary-like glands or related pluripotent germinative cells. Van der Putte et al previously suggested that the three categories should be unified.[3]

Previous case reports have described neuroendocrine differentiation in vulvar mucinous adenocarcinoma,[4,5,6] but there are no known cases of nonmucinous vulvar adenocarcinoma with neuroendocrine differentiation. We present a case and a review the literature. Only consent for treatment was obtained, and therefore the description has been de-identified to protect privacy.

Case:

A Hispanic woman in her early sixties presented to the Gynecology Oncology service for evaluation and treatment of vulvar squamous cell carcinoma diagnosed elsewhere. She had initially noticed a small bump on her right vulva 2-3 months prior to presentation. The lesion was described as 1.5-2 cm, located on the right labia majora, 2 cm from the midline. No further information was available from the initial presentation. At that time biopsy of the right labia majora reportedly showed invasive moderately differentiated non-keratinizing squamous cell carcinoma. The patient was questioned about possible neoplasia-related symptomatology. Patient complained of occasional bright red blood on her stool which was unchanged from previous years, but otherwise had no other symptoms including weight change, fevers chills, vulvar pain, pruritus, or discharge, nor did she report flushing or other manifestations of a neuroendocrine neoplasm. She had no relevant past medical or surgical history. Her last cervical cytology, 2 months before presentation, was reportedly normal. Physical examination in our clinic revealed the right labia majora with a healing biopsy site approximately 2.0 cm diameter, located 1.5cm from the midline. No masses or lymphadenopathy were appreciated. The remainder of the gynecologic examination was unremarkable.

The patient underwent right radical wide local vulvar excision with right inguinofemoral lymph node dissection which was uncomplicated, and was discharged home on POD#1. The patent was diagnosed with stage IIIB poorly differentiated vulvar adenocarcinoma with neuroendocrine differentiation(confirmed with a second pathologist) with positive inguinofemoral lymph nodes with extranodal extension.

Pathology:

The tumor was composed of solid sheets of infiltrating tumor cells with focal glandular structures(figures 1,2). Pagetoid spread into the overlying epithelium was present microscopically, but there was no clinical evidence of Paget's disease.(figure 3). Immunohistochemical stains were positive for: estrogen receptor, progesterone receptor, synaptophysin(consistent with neuroendocrine differentiation), CD56(focal, neuroendocrine differentiation), MOC31(consistent with glandular differentiation), P16 (50% staining); rare cells/weakly positive for: GCDFP-15, p63, ck7; and the tumor was negative for: mucicarmine, chromogranin, p40, BerEp4,CK20 and HMB45. Neuron specific enolase staining gave a faint inconclusive blush. Two out of five (2/5) inguinofemoral nodes had metastatic carcinoma, one with extranodal extension. The tumor measured 1cm wide, and 4mm deep. Lymphovascular invasion was present.

CT examinations of the chest, and of the abdomen and pelvis were negative for metastatic disease. The patient has undergone 6 weeks of radiation therapy of bilateral groin, pelvis and vulva with Cisplatin requiring a 2 week break due to vulvar desquamation. The sixth dose of Cisplatin was held due to neutropenia. She has also undergone chemotherapy with Carboplatin and Paclitaxel with Pegfilgrastim. She continues to present for regular follow up, and has no evidence of disease 8 months after surgery.

Discussion:

Primary vulvar adenocarcinomas are rare. There is still debate over the histological origins of these cancers. Extramammary Paget's disease (EMPD) is the most common of these adenocarcinomas, defined histologically as arising from apocrine, eccrine or anogenital mammary-like glands or related pluripotent germinative cells.[3] Only 20% are associated with invasion. They are positive for mucin, CK-7, CEA and Her-2-neu.[7] Sweat gland carcinomas, have been described as solid cords and tubular and/or adenopapillary structures. There is sometimes a pagetoid component [3] and are often associated with EMPD. [2] Rarer still are mammary-like adenocarcinomas, defined by presence of normal mammary-like glands near the tumor, a transition zone with malignant changes between normal and malignant tissue, presence of breast-like morphology, as well as expression of estrogen and progesterone receptors. [2]

We could find no case of neuroendocrine differentiation of an adenocarcinoma of the vulva in a nonmucinous lesion. The reported mucinous adenocarcinomas with neuroendocrine differentiation(4,5,6) showed tumor in pools of mucin, similar to pseudomyxoma peritonei, a totally different histology than our case. As the cell of origin in vulvar adenocarcinomas is not always elucidated, it cannot be determined if these are related neoplasms. A few case reports have described nonadenocarcinomatous neuroendocrine tumors of the Bartholin gland,[8,9] however these tumors were closely associated with the Bartholin gland itself, which is not the case here. Merkel cell carcinoma is also in the differential diagnosis as it is a neuroendocrine tumor, however Merkel cell carcinomas are not adenocarcinomas as well. Merkel cell carcinomas have been rarely reported in the vulva. They are aggressive neoplasms, sometimes

related to the Merkel cell polyoma virus, and stain for cytokeratin 20, which was negative in our case(10).

The cell of origin of the current case is unknown. Although there was Pagetoid spread of the tumor, no classic EMPD was identified adjacent to the carcinoma. Because it is the first such case we could find, expected behavior is uncertain as well. While some vulvar adenocarcinomas, such as mucinous adenocarcinoma, have behaved in an indolent fashion, some adenocarcinomas, such as invasive Paget's disease, can be aggressive. The presence of lymph node metastases, with extranodal spread, is concerning, hence leading to adjuvant therapy in this case. Our case showed focal gland formation, but much of the tumor was solid, giving it a "squamoid" appearance, which may have led to the initial diagnosis of squamous cell carcinoma. However, the immunoprofile of negative p40(a squamous marker) and positive MOC31(a glandular marker) along with focal gland formation confirmed that this tumor was an adenocarcinoma. Although unlikely, the possibility also exists of a collision tumor between a squamous cell carcinoma(removed initially) and an adenocarcinoma(11). As more of these unusual adenocarcinoma variants are reported, a more unified classification and prognostic factors will more likely become available.

Disclosures: none

Abbreviations and Acronyms

MOC31-anti-EPCAM antibody

P16 - p16 INK4a, a tumor suppressor gene

GCDFP-15,-Gross cystic disease fluid protein 15

p63-Gene that demonstrates squamous differentiation

ck7- Cytokeratin 7

p40- Gene that demonstrates squamous differentiation

BerEp4-Anti-EPCAM antibody

CK20 – Cytokeratin 20

HMB45- Human Melanoma Black 45

EMPD –Extramammary Paget's Disease

CEA-Carcinoembryonic antigen

Her-2-neu - Receptor tyrosine-protein kinase erbB-2

CT-Computerized axial tomography

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