Squamous Cell Carcinomas Arising From Adnexal Ductal Cysts

Henry G. Skelton, MD; Steven Flax, MD; Lawrence Chang, MD; Kathleen J. Smith, MD

- Malignant tumors arising from adnexal cysts are rare. We report 2 cases of squamous cell carcinomas that developed within cystic structures arising from adnexal ducts. An in situ hybridization technique for human papillomaviruses (HPV)-6/11, 16, 18, and 31, and immunohistochemical staining for p53 were performed. Both tumors showed focal expression of HPV-16 within areas showing squamoid changes and diffuse expression of p53 within the areas of invasive squamous cell carcinoma. Although nuclear staining for HPV has been identified in tumors of adnexal origin, to our knowledge these are the first cases in which a highly oncogenic HPV subtype, HPV-16, has been identified within squamous cell carcinomas arising from adnexal ductal structures. These cases may help explain primary cutaneous squamous cell carcinomas with no epidermal origin.

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Epidermal and apocrine hidrocystomas are eccrine- and apocrine-derived cysts, which most investigators consider to be ductal malformations and not benign neoplasms. Herein, we report 2 unusual cases involving the development of squamous cell carcinomas (SCCs) arising from adnexal cysts.

In situ hybridization showed focal nuclear staining for human papillomavirus (HPV)-16 in the squamous epithelium that arose within both cysts. Although HPV has been detected in the eccrine ducts in syringocystadenoma papilliferum, the oncogenic HPV-16 virus has not previously been associated with the development of SCCs arising from adnexal ductal structures. Within the areas of SCC, both tumors showed diffuse expression of p53.

REPORT OF CASES

Case 1

An 85-year-old white man presented with a nodule on the left temple that had been evident for an undetermined period and that had recently enlarged rapidly. Clinically, the nodule was ill-defined, fixed, and did not appear to involve the overlying epidermis. A malignant tumor was suspected, and the nodule was excised.

Hematoxylin-eosin-stained sections were examined. The biopsy specimen showed cystic dilatation of a 2-cell-layer ductal structure that arose from a benign follicular structure at the level of the upper reticular dermis. The 2-cell-layer epithelium appeared bland at its origin. This epithelium merged into a multilayered epithelium and then became more squamoid, showing hyperkeratosis and cytoplasmic atypia that became markedly pleomorphic with peripheral extension into the dermis (Figures 1 through 3). The atypical squamous cells formed a large tumor mass infiltrating deep and laterally with a dense inflammatory reaction. The overlying epidermis showed no cytoplasmic atypia; however, there was moderate solar elastosis.

A diagnosis of SCC arising from an adnexal ductal structure was made. The tumor was re-excised to clear the margins, and there was no evidence of recurrence at 54 months.

Case 2

An 80-year-old white man presented to his dermatologist with a subcutaneous mass on the left cheek that had been present for several weeks. There was no history of a prior lesion. The clinical impression was a cystic lesion with no evidence of epidermal involvement. The lesion was excised and submitted for routine pathologic examination.

Hematoxylin-eosin-stained sections were examined. The biopsy specimen showed a cystic tumor arising from a dilated eccrine duct (Figure 4). The initially cuboidal ductal epithelium showed progressive squamoid changes with hyperkeratosis within an area of cystic dilatation. Lateral and deep, these squamoid areas showed marked pleomorphism and cytoplasmic atypia with infiltration into the surrounding tissue (Figure 5). The inflammatory reaction to this tumor was marked in areas. The overlying epidermis showed no significant cytoplasmic atypia; however, there was dermal solar elastosis. A diagnosis of SCC arising from an eccrine duct was made, and the area was re-excised with clear margins. There was no evidence of recurrence or metastasis after 12 months.

IMMUNOHISTOCHEMICAL STUDIES

In situ DNA probes (Pathgene-Enzo Diagnostics, Syosset, NY) for HPV types 6/11, 16, 18, and 31 were performed using standard techniques as supplied by the manufacturer. The in situ DNA probe for HPV-16 was focally positive within both tumors in squamoid areas (Figure 6). No positive nuclear staining was seen within the 2-cell-layer areas of the cyst wall or within other eccrine ducts seen within either biopsy specimen. The same in situ HPV DNA probes were performed using the same technique on 3 eccrine hidrocystomas, 3 eccrine syringomas, 2 eccrine poromas, and 3 apocrine hidrocystomas; none showed any positive staining.

Immunohistochemical studies for the monoclonal antibody (1:50; BioGenex, San Ramon, Calif) and p53 (DO7; Squamous Cell Carcinomas From Adnexal Ductal Cysts—Skelton et al.
COMMENT

We were unable to find any similar reports of SCCs arising from simple adnexal ducts. Squamous cell carcinomas arising from adnexal ductal structures such as these could explain the occasional occurrence of SCCs found in the dermis without an epidermal origin. The squamoid histologic changes within the cyst lining and the identification of HPV-16 by in situ hybridization implicate this oncogenic HPV in the development of these SCCs. There is a known association between several types of HPV and neoplasia in the uterine cervix, and a suspected relationship at other sites.5-7 HPV-16 has been found in SCCs arising in genital skin, oral mucosa, and the nail bed, and less commonly in cutaneous SCCs from other sites, especially in immunosuppressed hosts or in patients undergoing psoralen plus ultraviolet light of A wavelength therapy.5-7 However, other than age-related changes in immunity, neither of these patients had known immunosuppression, and neither patient had undergone psoralen plus ultraviolet light of A wavelength therapy or other immunosuppressive therapies.

Perhaps a moist environment, which has been proposed to predispose to the development of hidrocystomas, and/ or an underlying ductal abnormality that resulted in the cystic space itself could produce an environment that would allow for survival and proliferation of this oncogenic HPV subtype. It is possible that a hidrocystoma was infected by HPV. The HPV alone or with other unknown oncogenic factors may have lead to squamous metaplastic changes that progressed with subsequent molecular changes to SCCs.

Two viral early genes, E6 and E7, and an upstream regulatory region are believed to be responsible for the HPV-induced oncogenic events.8 E6 and E7 are transcribed from a promoter, P97, and P97 is regulated by complex interactions between multiple positive and negative cel-
lular factors and the viral E2 product. E2 disruption with integration leads to dysregulation and overexpression of E6 and E7. E6 protein binds to and promotes the degradation of the tumor suppressor protein, p53, while the E7 protein complexes the Rb protein, inhibiting its cell-cycle regulatory effects. The effects of E6/E7 expression on cell-cycle regulatory proteins are to increase levels of cyclin E, cyclin D1, Cdk4, and Cdk6, as well as p53, p21, and p27. Thus, the major response with integration appears to be secondary to E7, and this response would explain the increased expression of p53 even in the presence of increased degradation induced with E6 binding. This broad spectrum of cell-cycle dysregulation with integration of HPV-16 may explain the induction of mutations via p53-independent as well as p53-dependent mechanisms, including the activation of telomerase by p53 for immortalization of tumors.

References