Pseudoglandular (adenoid, acantholytic) squamous cell carcinoma of the penis. A case report

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SUMMARY
A case of so-called pseudoglandular (adenoid, acantholytic) squamous cell carcinoma (SCC) of the penis occurring in a 60-year-old man is described. The tumor showed, in addition to the pattern of conventional moderately to poorly differentiated SCC, a component of tubular-appearing pseudoglandular SCC. No precancerous dysplastic lesion was found near the lesion. Immunohistochemically, the tumor cells expressed pancytokeratin, p53 and p63, and they were negative for endothelial markers, carcinoembryonic antigen and p16. Stains for mucin were negative. Metastases were found in the regional lymph nodes and spermatic cord. Four weeks after the nephrectomy, multiple cutaneous/subcutaneous metastases appeared and metastases in the pelvic lymph nodes were visualized through a CT scan. The advanced stage of the tumor seen in the present case further confirms that pseudoglandular SCC represents a highly aggressive tumor.

Key words: adenosquamous carcinoma · pseudoglandular (adenoid, acantholytic) squamous cell carcinoma · penis · p16 · p53

ORIGINAL ARTICLE

Pseudoglandulárny (adenoidné, akantolytické) dlaždicovobunkový karcinóm penisu. Popis prípadu

SÚHRN

Kľúčové slová: adenosquamózny karcinóm · pseudoglandulárny (adenoidný, akantolytický) dlaždicovobunkový karcinóm · penis · p16 · p53

So-called pseudoglandular (adenoid, acantholytic) squamous cell carcinoma is a rare type of squamous cell carcinoma (SCC) that was described in the skin (1-3), oral cavity (4), breast (1,5), lung (1,6), bladder (7), uterine cervix (8) and vulva (7,8). In the penile location, pseudoglandular SCC was described quite recently by Cunha et al. (9). The tumor represents a highly malignant type of penile squamous cell carcinoma (SCC) that contains a tubular-appearing acantholytic pattern strongly mimicking adenocarcinoma. After the first publication, two further cases were added by Co-lecchia and Insabato (10). Because no additional reports were published, we would like to present our recent case of this rare tumor.

MATERIALS AND METHODS
The tissue of the excised tumor was fixed in 4% formalin and processed routinely. The sections were stained with hematoxylin and eosin, PAS, PAS with diastase pretreatment, alcian blue at pH 2.5, and mucicarmine. Following primary antibodies were used for immunohistochemistry: p53 (clone DO-7), CD31 (JC70A), epithelial membrane antigen (EMA, E29), carcinoembryonic antigen (CEA, II-7) (all from Dako Cytomation), and p16 (JC8), pancytokeratin (AE1/AE3), CD34 (Qbend 10) (all from LabVision). Immunostaining was performed according to the standard protocols using avidin-biotin complex labeled with peroxidase or alkaline phosphatase. Microwave antigen pretreatment was performed prior to applying the primary antibodies with exception of CD34. Appropriate positive and negative controls were applied.

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A 60-year-old man with arterial hypertension and type 2 diabetes mellitus presented with a large irregular white-gray tumor occupying right half of the glans penis. The tumor grew over several months. After the diagnostic excision confirming SCC, complete penectomy with bilateral inguinal node dissection was performed. Four weeks after the penectomy, multiple cutaneous/subcutaneous metastases in pubic, bilateral inguinal and bilateral anterior/medial femoral regions appeared. Three of the cutaneous/subcutaneous lesions were excised and histopathologically examined. In addition, a CT scan revealed multiple metastases in the pelvic lymph nodes. The patient was started on radiotherapy. However, this therapy was ineffective because new lenticular cutaneous metastases appeared. Therefore, the radiotherapy was discontinued and the patient was started on palliative chemotherapy (cisplatin, 5-fluorouracil). The possibility of additional radiotherapy will be considered later.

Grossly, the tumor was ulcerated and flat, invading 3 cm deep into the corpus cavernosum. Moreover, numerous satellite nodules were seen in the corpus cavernosum, some of them even near the proximal resection margin. Histologically, the tumor showed two intermingled components (Fig. 1). The first was conventional, moderately to poorly differentiated squamous cell carcinoma without koilocytic features (11,12), and the other showed a pseudoglandular pattern with cuboidal to cylindrical epithelium (Fig. 1A,B). The nuclei of the pseudoglandular epithelium were highly atypical and possessed frequent mitotic figures. The cells were arranged in pseudoglands to

Figure 1. Histologic findings: (A) pseudoglandular pattern and pattern of common squamous cell carcinoma, (B) adenoid structure mimics tubular adenocarcinoma, (C) rare area of diffuse infiltration in the stroma, (D) early acantholysis in the nest of common squamous carcinoma cells, (E) hyperplastic epidermis near the tumor margin (hematoxylin and eosin, original magnifications x25, x200, x200, x100, x100; respectively)
ward the luminal space. Some of the spaces contained necrotic debris or non-specific eosinophilic material. Gradual transitions were seen between both components. In rare foci, isolated neoplastic cells or small groups of the cells diffusely infiltrated the penile stroma (Fig. 1C). The squamous cell nests showed focally, in addition to small adenoid spaces, early acantholysis with intercellular edema and dyscohesion of the cells. This indicated that formation of pseudoglandular spaces represents a result of acantholysis (Fig. 1D). The conventional SCC- and pseudoglandular components comprised 40% and 60% of the tumor volume, respectively. The tumor was deeply invasive, with infiltration of the corpus cavernosum. A few foci of vascular or perineural invasion were found. The tumor grew discontinuously with formation of satellite nodules. The cutaneous margin of the lesion showed epidermal hyperplasia without atypia, and non-specific dermatitis without features of lichen sclerosus (Fig. 1E). Features of penile squamous intraepithelial neoplasia or other known precursor lesions (bowenoid, pagetoid) (11,13,14) were not found. Small 4 mm sized tumor infiltrate was found in a connective tissue of the spermatic cord, with obvious peri- and intraneural tumor spread. There was a 2.5 cm large metastasis in one of the right-sided inguinal lymph nodes. The other three right inguinal nodes and the ten left inguinal nodes lacked metastasis. The lymph node metastasis and all three excised 0.5-1 cm sized cutaneous/subcutaneous metastases also showed microscopically both pseudoglandular and conventional SCC patterns. Stains for mucin were negative in the neoplastic cells as well as in the adenoid spaces. Immunohistochemically (Fig. 2), the tumor cells expressed strongly and diffusely pancytokeratin AE1/AE3, p63 (not shown) and p53, and they were negative for p16, CEA, EMA, CD31 and CD34.

**DISCUSSION**

The present case of pseudoglandular SCC shows morphologically all features described in previous studies of this rare entity (9,10). A high stage and grade appear to be typical for this tumor type according to previous reports (9,10). Our observation is similar, and thus it confirms that pseudoglandular SCC represents, along with sarcomatoid carcinoma, a tumor of the highest malignant potential in the group of penile carcinomas. All published cases together with the present case show that 6 of 10 (60%) patients had regional lymph node metastasis, and 4 of 10 patients (40%) died from the disease. At the histologic level, the poor prognosis of the tumor is indicated by high-grade nuclear features and frequent vascular and/or perineural invasion, which were seen also in our case.

Regarding the natural history of pseudoglandular SCC, Cunha et al. found near the tumor margin low-grade intraepithelial squamous lesion (intraepithelial penile neoplasia, differentiated) in 4 of 7 cases (9). Thus, it seems that the precursor lesion for penile pseudoglandular SCC is differentiated intraepithelial penile neoplasia which is not HPV-related (11). Although additional cases, including the present tumor, showed only a hyperplastic lesion without atypia near the tumor margin (9,10), it is quite possible that the precursor lesion was overgrown by the invasive tumor, because the tumors were large at their first presentation. Immunohistochemical negativity of p16 found in our case further suggests that the tumor is not HPV-related (15). Ancillary studies of HPV in acantholytic SCCs (without regard to the location of the tumor) also showed negative results, although available data remain very scanty at present. In one case of penile acantholytic SCC, in situ hybridization showed no positivity for HPV (16). In another case of vulvar adenoid SCC, Horn et al. did not find the viral DNA (17).

In the differential diagnosis, the pseudoglandular morphology strongly mimics the tubular pattern of an adenocarcinoma or the vascular channels of an epitheloid angiosarcoma. Negative stains for mucin prevent misdiagnosis of an adenocarcinoma or adenosquamous carcinoma. Negativity of endothelial markers (versus positivity of cytokeratins and p63) and the presence of conventional squamous cell component are helpful for the differentiation from the epitheloid angiosarcoma.

In conclusion, we have described an additional case of a pseudoglandular SCC of the penis. Our findings indicate, similarly to those described in previous studies, that the tumor is a highly aggressive type of SCC, and that it is probably not HPV-related. Pathologists should be familiar with this entity because it shows distinct clinical features and prognosis, and, by histologic examination, it can mimic other penile tumors.

![Figure 2. Immunohistochemical findings (A) expression of pancytokeratin AE1/AE3, (B) p53 positivity, similar strong diffuse reactivity gave also p63 antibody (original magnifications x100 and x25; respectively).](image-url)
REFERENCES