Case report

Skene's gland adenocarcinoma coexisting with infiltrating urothelial carcinoma of the urinary bladder

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A 78-year-old woman underwent radical cystectomy due to high-grade infiltrating urothelial carcinoma of the urinary bladder. Histopathological examination of the bladder neck revealed coincidental urothelial carcinoma and tubular neoplasm resembling prostatic acinar adenocarcinoma. The latter was accompanied by a non-invasive component showing features of high-grade prostatic intraepithelial neoplasia (PIN). The lesion showed immunopositivity for prostate-specific antigen, prostein, and androgen receptor. The diagnosis of Skene's gland adenocarcinoma (SGA) was established. This is the 14th case of SGA in the literature, and the first coexisting with urothelial carcinoma. Our case demonstrates a possible origin of SGA from precursors resembling PIN.

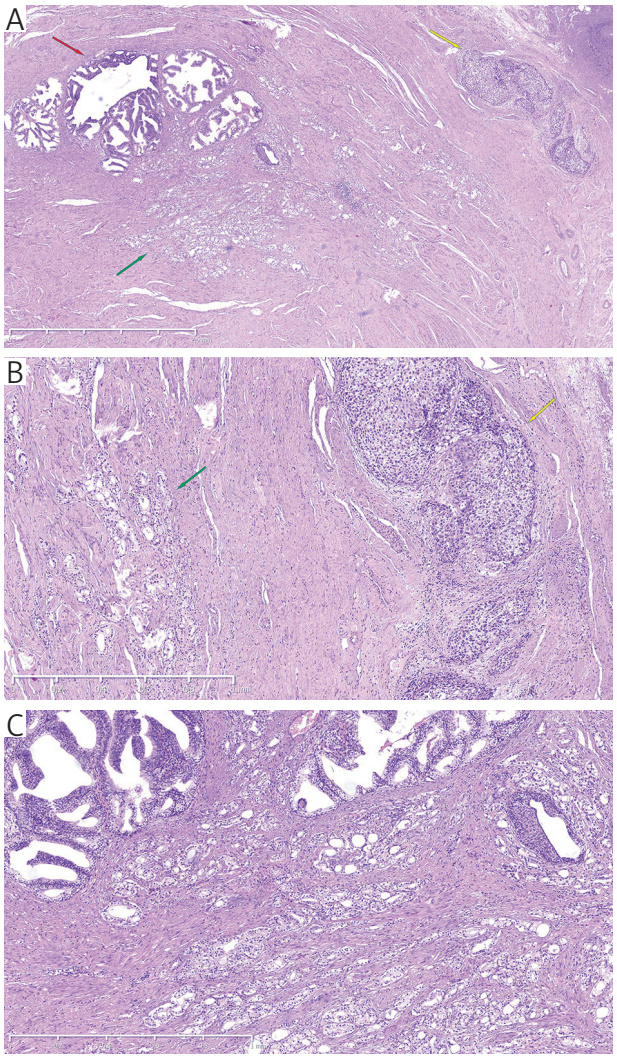
Key words: Skene's gland adenocarcinoma; prostate cancer, prostate intraepithelial neoplasia, immunohistochemistry.

Introduction

Skene's glands, also known as periurethral glands or "female prostate", are located near to urethral meatus, empty into the vaginal vestibule, and provide lubrication for sexual intercourse. In terms of embryology, Skene's glands are homologous to the male prostate. They are lined by two layers of cells: apical columnar or cuboidal cells (secretory layer) and basal cells (reserve layer) [1, 2]. Both of them express prostate-specific antigen (PSA), and the source of PSA in female serum and urine [1].Skene's gland adenocarcinoma (SGA) is an extraordinarily rare malignancy with 13 cases described to date, including a series of 4 cases published recently by Tregnago and Epstein [3, 4, 5, 6, 7, 8, 9, 10, 11, 12]. Thus, we would like to report a unique case of a microscopic SGA discovered incidentally after a cystectomy that was performed due to infiltrating urothelial carcinoma of the bladder.

Case report

A seventy-eight-year-old female patient was admitted to the Urology Department of University Clinical Center Hospital in Gdańsk, Poland, due to suspicion of a bladder malignancy. She had been experiencing hematuria and dysuria for the past several months. An ultrasound scan revealed a hypervascular mass measuring up to 71 mm, adjacent to the left lateral wall of the bladder, and the left part of the trigone. The left ureter, renal calyces, and pelvis were dilated. Magnetic resonance imaging (MRI) suggested transmural invasion. The tumor mass was papillary in nature, contrast-enhancing, and presented prominent decreased diffusion in the arterial phase. Subsequently, an uneventful radical cystectomy was performed. Histopathological examination of the obtained material revealed high-grade infiltrating urothelial carcinoma, with deep invasion of the bladder wall. There was also microscopic invasion of the perivesical adipose tissue, vaginal stroma, uterus, and regional



red arrow – prostate intraepithelial neoplasia (PIN)-like elements; green arrow – invasive Skene's gland adenocarcinoma component; yellow arrow – infiltrating urothelial carcinoma

Fig. 1. Low-power (A) and high-power (B) of Skene's gland adenocarcinoma (left) coexisting with nests of infiltrating urothelial carcinoma (upper right); C) Neoplasm is mainly composed of fused and coalescent glands; prostate intraepithelial neoplasia (PIN)-like elements are visible

lymph nodes (pT4aN2). Vascular invasion was prominent. In the bladder neck, besides the foci of urothelial carcinoma, a distinctive neoplastic infiltrate was identified. It measured 3 mm in its largest dimension and was composed of the coalescent and fused glands morphologically resembling acinar adenocarcinoma, Gleason grade 4+3=7 (Gleason group 3), and complex glands resembling the cribriform and micropapillary pattern of high-grade prostatic intraepithelial neoplasia (PIN) (Fig. 1). High molecular weight cytokeratin (HMWCK), GATA3, p63, and p40 stainings showed a basal cell distribution in the PIN-like component and were completely negative in invasive elements. Both components showed positive staining with prostate-specific antigen (PSA), prostein, androgen receptor (AR), and CAM 5.2, but were negative for α-methylacyl-CoA racemase (AMACR), erythroblast transformation-specific [ETS]-related gene (ERG), cytokeratin 7 (CK7), cytokeratin 19 (CK19), cytokeratin 20 (CK20), estrogen receptor (ER), and GATA3. On the other hand, adjacent PIN-like glands showed focal strong CK19 staining. The focus of the infiltrating urothelial carcinoma was positive for HMWCK, CAM 5.2, CK19, CK20, p40, p63, and GATA3, and negative for prostatic markers. The summary of immunohistochemical results is shown in Table I. Eventually, the diagnosis of SGA coexisting with infiltrating urothelial carcinoma was established.

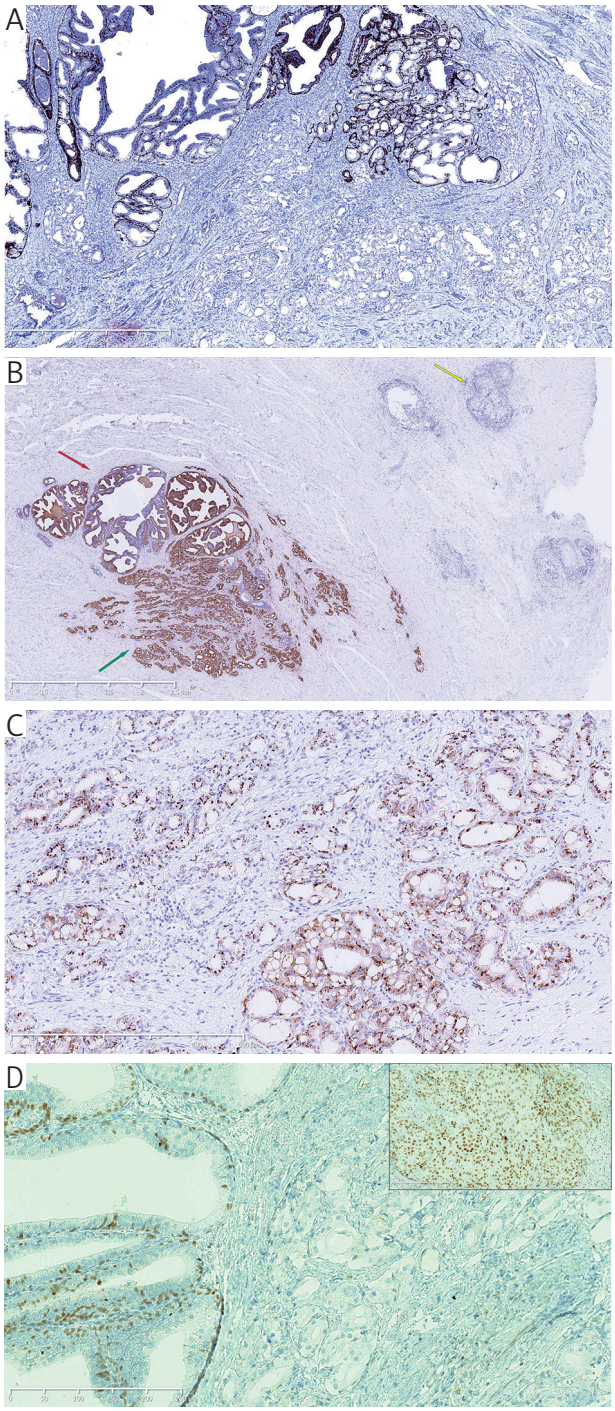
Table I. The summary of immunohistochemical results in Skene gland adenocarcinoma (SGA) and urothelial carcinoma (UC)

Marker	SGA	UC
Prostein	Positive	Negative
PSA	Positive	Negative
AR	Positive	Negative
ERG	Negative	Negative
AMACR	Negative	Negative
CK19	Focally positive	Positive
CK20	Negative	Positive
CAM 5.2	Positive	Positive
HMWCK	Positive in basal cells of PIN-like elements; negative in invasive component	Positive
p63	Positive in basal cells of PIN-like elements; negative in invasive component	Positive
p40	Positive in basal cells of PIN-like elements); negative in invasive component	Positive
GATA3	Positive in basal cells of PIN-like elements; negative in invasive component	Positive

PSA – prostate specific antigen; AR – androgen receptor; ERG – ETS-related gene; AMACR – α-methylacyl-CoA racemase; CK – cytokeratin; HMWCK – high molecular weight cytokeratins; PIN – prostatic intraepithelial neoplasia

Discussion

In males, it is not uncommon to see coincidental bladder urothelial carcinoma and prostate acinar adenocarcinoma after cystoprostatectomy [13]. In various studies, the frequency of this combination ranges from 2 to 58% [14]. In particular, the concomitance between these two malignancies is higher than the rate of either one in the general population, suggesting a potential pathogenetic link. Nevertheless, the coexistence of SGA and urothelial carcinoma



red arrow – prostate intraepithelial neoplasia (PIN)-like elements; green arrow – invasive Skene's gland adenocarcinoma component; yellow arrow – infiltrating urothelial carcinoma

Fig. 2. The results of immunohistochemical staining: A) prostate intraepithelial neoplasia (PIN)-like elements express HMWCK, and invasive component is negative; B) intense PSA stain in Skene's gland adenocarcinoma and PSA-negative nests of urothelial carcinoma; C) positive prostein stain in invasive Skene's gland adenocarcinoma component; D) GATA3 positive staining in basal cells of PIN-like elements and negative in invasive component; inset shows diffuse nuclear GATA3 staining in urothelial carcinoma

has not yet been reported. Two out of 13 previous cases had a history of malignancy treated with radiation (ovarian and cervical carcinoma) and one autopsy case showed synchronous renal cell carcinoma [3]. Our case is the first one diagnosed incidentally and without a macroscopically visible lesion. Therefore, it is possible that the frequency of SGA is higher, but small and well-differentiated lesions might be clinically insignificant, which is similar in the case of low-volume, low-grade prostate cancers in elderly male patients. Interestingly, the majority of SGA cases were described in elderly patients and had a favorable clinical course without metastases. Only one case, diagnosed in a relatively young patient (46-year-old), metastasized to regional lymph nodes [11]. In males below the age of 55, frequently aggressive forms of prostate carcinomas are present. [15]. Due to its scarcity, it is uncertain if prognosis in SGA depends on the patient's age or other factors, such as the Gleason score. Nevertheless, the most common Gleason pattern seems to be 4 + 4 = 8, often with cribriform tumor architecture [3]. Another similarity associated with prostate cancer is an elevated PSA level in serum, which is a useful clue indicating the presence of a primary paraurethral neoplasm in females, and its decline may serve as a marker of successful therapy [8]. Unfortunately, in our case, PSA levels were not measured due to the lack of preoperative clinical suspicion of SAG.

Positive immunohistochemical stains in SGA reported in prior literature include PSA, prostate-specific acid phosphatase (PSAP), NKX3.1, prostein, AMACR, and CK7. One case showed ER expression, and did not express any available prostatic markers, but retained prostatic acinar adenocarcinoma-like morphology [3]. Moreover, CK20 and CDX2 positivity were reported in two cases displaying intestinal differentiation [4]. Hereby, we report AR as one more positive immunohistochemical marker of SGA but it requires further validation. Immunostains for p40, p64, and HMWCK were positive in basal cells of PIN-like elements, and a similar staining pattern was observed in the *in situ* component of some other cases of SGA [3]. Furthermore, our case suggests that these markers, together with GATA3, are effective in differentiating urothelial carcinoma and SGA.

Murphy *et al*. suggested that there are three potential origins of urethral adenocarcinoma development: urethritis glandularis (mucinous adenocarcinoma), Skene's gland (adenocarcinoma resembling male prostate cancer), and the third unknown pathway leading to the formation of clear cell carcinoma [10]. We demonstrate the co-occurrence of obvious high-grade PIN-like component, which may support the step-wise fashion development of SGA from precursor lesions, as in the male prostate.

The differential diagnosis of urethral carcinomas is important since the above-mentioned cancers tend to be more aggressive than Skene's gland adenocarcinoma. Potential diagnostic pitfalls include focal mucinous differentiation in Skene's gland adenocarcinoma and occasional expression of prostate antigens by clear cell carcinoma [16]. Moreover, prostatic tissue reactive with anti-PSA antibodies may exceptionally appear in the female genitourinary tract, i.e. in the uterine cervix, ovarian cystic teratoma, or ovarian mesonephric nests [17–19]. Interestingly, a unique case of evident prostatic adenocarcinoma arising in ovarian teratoma has been described [18]. Skene's gland lesions have also been described in the vagina (tubulo-squamous polyp) [20].

Conclusions

We have described a unique case of incidental Skene's gland adenocarcinoma accompanied by a high-grade PIN-like component synchronous with infiltrating urothelial carcinoma of the urinary bladder. This combination has not been previously reported in the literature. This coincidence may indicate a common pathogenetic pathway of the cancerogenesis in Skene's gland and urinary bladder, however, this hypothesis requires further studies.

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