CASE REPORT

Urothelial carcinoma and prostatic adenocarcinoma presenting as collision tumors

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Urothelial carcinoma (UC) and prostatic adenocarcinoma (PAC) commonly occur in elderly patients and share common carcinogenic factors that could be identified in the urine. The presence of one tumor is known to be associated with an increased incidence of the other. Simultaneous occurrence of PAC and UC in the prostate is not uncommon; however, urinary bladder location of both lesions has not yet been reported. Furthermore, invasion into the urinary bladder wall by a PAC can also pose a diagnostic challenge with UC and other primary urinary bladder tumors.

We report three patients presenting with UC and PAC within the urinary bladder. The patients were 80, 84 and 85 years old. All patients were diagnosed with high grade PAC and either had simultaneous at the initial diagnosis or developed UC during the follow up for PAC. Histopathological analysis pictured collision tumors consisting of an invasive component represented by high grade PAC and a superficial component composed of low or high grade UC. Both components displayed distinctive immunophenotypes: PAC was P63- /HMWCK- /PSA+ and UC was p63+/HMWCK+/ PSA-.

In conclusion, awareness of this association is important in making the correct diagnosis, especially when dealing with urinary bladder biopsy material.

Key Words: urothelial, prostatic, carcinoma, urinary bladder

Introduction

In male patients, prostatic adenocarcinoma (PAC) is the most prevalent cancer and bladder urothelial carcinoma (UC) is also a frequent malignancy. The incidence of PAC in radical cystectomy specimens for invasive bladder cancer has been noted to be in the range of 35% to 70%.[1] A recent study demonstrated a statistically significant association between PAC of the prostate and UC of the urinary bladder.[2] Advanced stage PAC of the prostate often involves the urinary bladder. Despite this known relationship, urinary bladders showing both PAC and UC have not been described. We report three such cases.

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Case report

Case 1 is an 80-year-old male with a history of PAC treated by radiotherapy and subsequently by hormonal therapy 6 years previously. The patient recently presented with rising prostatic specific antigen (PSA) titre of 4-5 ug/l and gross hematuria and extensive bony metastases. Magnetic resonance imaging demonstrated extensive bony metastatic disease on the right side of the pelvis. The prostate showed no interval enlargement and remained well-defined. The transurethral cystoscopic evaluation demonstrated an area of mucosal irregularity on the left side of the trigone. A biopsy of the mass was performed, the patient died of metastatic disease 2 years later.

Case 2 is an 84-year-old male with a history of urinary frequency. Digital rectal examination demonstrated a firm, but mobile and nontender prostate and serum PSA was 9.11 ug/l. Transurethral cystoscopic examination revealed two tumors one large sessile tumor, 1.5 cm in diameter, at the bladder dome and the other one, 1.0 cm in diameter, at the bladder neck. Both tumors were sampled for histopathological assessment. Subsequently, a 10-core transurethral biopsy was performed to rule out the prostatic adenocarcinoma. The patient received androgen ablation therapy in the form of Lupron. One year after resection his serum PSA was 2.79 ug/l and there was no evidence of clinical metastatic disease.

Case 3 is an 85-year-old male with a history of cribriform PAC on needle prostatic biopsy treated with hormonal therapy and radiotherapy. The patient developed lower urinary symptoms with hematuria on the fifth year of follow up. Serum PSA level was 4.6 ug/l, but clinical work up revealed no evidence of metastasis. Digital examination revealed an enlarged, firm and fixed prostate. Cystoscopy was performed and revealed a small papillary lesion in the trigone. There was no papillary lesion in the prostatic urethra. Follow up cystoscopy at 1 and 2 years later revealed recurrence of the urinary bladder lesions. All papillary lesions were biopsied. The patient died of unrelated disease 4 months after the last biopsy.

In all cases, the biopsy or resection specimens revealed high grade PAC associated with papillary UC in a collision tumor pattern. In the first case, the specimen displayed PAC composed of nests and fused glands with a Gleason score of 4 + 4/10 in the submucosa. The urothelial mucosa overlying the PAC showed a noninvasive and low grade UC, Figures 1a and 1b. In the second case, the specimen from the bladder neck showed a poorly differentiated PAC with solid and cribriform architecture (Gleason score of 5 + 4/10. The bladder dome lesion showed a collision tumor pattern with a noninvasive papillary high grade UC and areas of PAC similar to that seen in the bladder neck, Figure 2a. The prostatic biopsy showed no evidence of carcinoma. In the third case, three out of five biopsy fragments were involved by a noninvasive low grade UC and the remaining two fragments by a cribriform PCA. Subsequent biopsies showed the recurrent low grade UC. There was no evidence of PCA in the latter two biopsies.

The pattern of immunohistochemical staining was similar in all three cases. In all cases, PAC showed focal and weak to moderate reactivity for PSA (Dako, Glostrup, Denmark, dilution 1:100) and was negative for HMW CK (clone 34betaE12) (Dako, dilution 1:100) as well as p63 (Dako, dilution 1:100). CK20 immunostaining showed

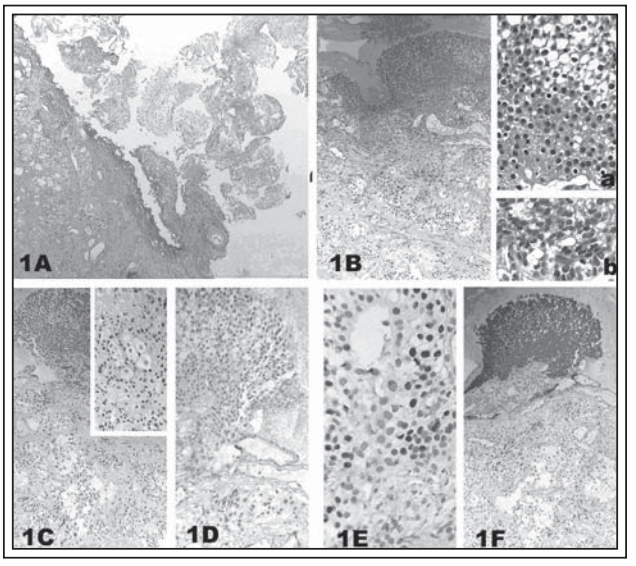

Figure 1. Case 1: Collision tumors with papillary UC (upper portion of the micrograph) and PAC (lower portion).
1a. The transurethral resection specimen showing the low grade papillary UC (upper right) and the PAC (lower left).
1b. A high magnification showing the papillary UC on the surface of the urinary bladder and the PAC in the underlying stroma in the same tissue fragment, in a collision tumor pattern. Inset a: a high magnification of the UC, b: a high magnification of the PAC.
1c. Immunostaining for PSA showing negative reactivity in the UC component and weak reactivity in the PAC component. Inset: a high magnification.
1d. Immunostaining for CK20 showing weak reactivity in both UC and PAC components.
1e, 1f. Immunostaining for p63 (nuclear reactivity) and HMW CK showing strong and diffuse reactivity in the UC component and negative reactivity in the PAC component.

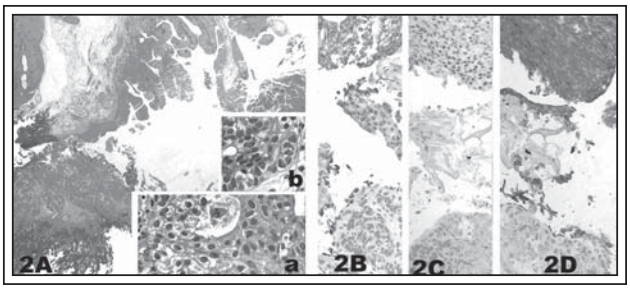

Figure 2. Case 2: The papillary UC (upper portion of the micrograph) and PAC (lower portion).
2a. The transurethral resection specimen showing the noninvasive high grade papillary UC (upper half) and the PAC (lower haft). Inset a: a high magnification of the UC, b: a high magnification of the PAC.
2b. Immunostaining for CK20 showing strong reactivity in the UC component and negative reactivity in the PAC component.
2c, 2d. Immunostaining for p63 (nuclear reactivity) (c) and HMW CK (cytoplasmic) (d) showing strong and diffuse reactivity in the UC component and negative reactivity in the PAC component+.

negative or focal weak reactivity in urothelial cells undermining umbrella cells in case 3 and 1 respectively, and negative reactivity in case 2. The UC stained strongly and diffusely for HMW CK and p63. They were negative for PSA in all three cases, Figures 1c-1, 2b-2d, and 3.

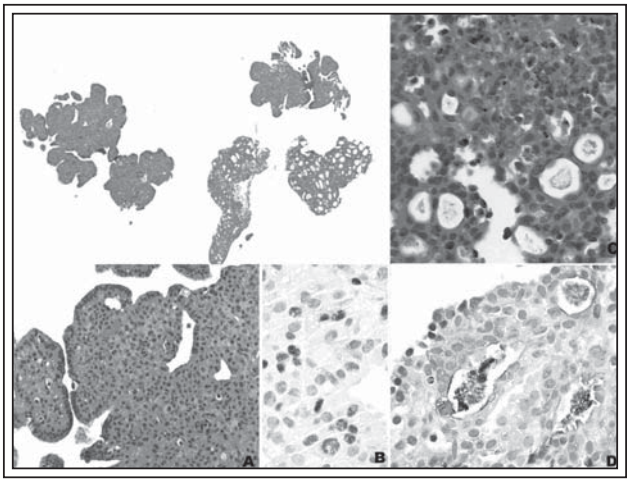

Figure 3. Case 3: Three fragments of noninvasive papillary UC and two fragments of PAC (arrows).
3a, 3b. Medium magnification of the noninvasive low grade papillary UC showing positive immunoreactivity for p63.
3c, 3d. High magnification of PAC showing positive immunoreactivity for PSA.

Discussion

In this report, PAC and UC were distinguished by the cribriform architecture of the PAC and the papillary architecture of the UC. Reactive hyperplasia and atypia caused by previous radiotherapy (case 1 and 3) were excluded in view of the severe degree of atypia and the papillae formations.

In the cases described, occurrence of both PAC and UC in the same pathology material can represent a diagnostic challenge to the surgical pathologist. Glandular or mucinous differentiation in high grade UC, either in a pure pattern or in a mixed glandular urothelial pattern, can resemble greatly PAC. Furthermore, high grade PAC usually shows minimal gland formation, therefore mimicking UC, especially in patients treated by hormonal therapy.[3] Invasion into the urinary bladder wall by PAC can also be difficult to distinguish from other urinary bladder tumors. In PAC presenting with an acinar architecture, other primary lesions of the urinary bladder including: nephrogenic adenoma[4] and mucinous or mesonephric adenocarcinoma[5] are to be considered. Immunostaining for PSA, prostatic acid phosphatase (PAP), Leu-7, thrombomodulin, uroplakin, cytokeratin 7, HMW CK, clone 34betaE12, and p63 have been used to distinguish high grade PAC from UC.[6,7] PSA appeared to be specific and reactive for PAC in up to 95% of cases whereas HMW CK and p63 were specific for UC and were reactive for UC in 100% and 95% of cases, respectively.[8-10] As previously reported, our series showed that immunohistochemistry played a pivotal role in establishing an accurate distinction between the two pathological entities.

High grade PAC involving the urinary bladder represents secondary involvement of the latter by a prostate cancer, as illustrated by our first case. The second case of our series presented an interesting problem, since the patient did not have previous history of PAC. Although PAC in this patient likely represents a secondary spread from a prostate primary arising from the uppermost portion of the prostate (central or transition zones), the possibility of a primary PAC arising from the bladder neck can not be excluded as the neoplasm was cystoscopically seen in this area. Primary PAC of the urinary bladder has been reported previously.[11]

The simultaneous occurrence of these two malignancies in the urinary bladder is an uncommon phenomenon and has not been reported previously. This peculiar association may be attributed to: a) the patient's advanced age, as seen in all three cases reported in this series, and b) the presence

of common carcinogenic factors detectable in the urine, as suggested by Singh.[2] Patients with double malignancies have been shown to have higher frequency rapid genotypes of N-acetyltransferase (NAT), an enzyme known to activate carcinogenic amines. NAT2 is a slow acetylator genotype which recently has been demonstrated to be an important risk for development of PAC in Japanese men.[12] There is an association between NAT2 slow genotype and an increased risk of urothelial carcinoma[13] as well. Studies have shown that genetic mutation of p53 and RB genes were involved in the development of these two malignancies. Common carcinogenetic pathways or the presence of associated chronic inflammatory insult are possible mechanisms that increase the risk of PAC in male patients presenting with UC, or vice versa.

In conclusion, we reported three cases of PAC and UC which presented as collision tumors within the urinary bladder, and propose a possible histopathogenetic association between these two entities. Awareness of this association is important in making the correct diagnosis, especially when dealing with urinary bladder biopsy material. □

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