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Synchronous Triple Distinct Urological Tumors in a Patient: Urothelial Carcinoma of Bladder, Unilateral Renal Oncocytoma and Papillary Adenoma

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Abstract Synchronous multiple primary tumors of the urinary tract are quite rare. The medical literature refers to a small percentage (around 4%) of the incidence of oncocytomas synchronous with other kidney tumors as renal cell carcinoma, pelvic urothelial carcinoma, angiomyolipoma etc. Papillary adenoma is one of those tumors that may rarely coexist with oncocytoma. In this study, we present a case of 69-year-old male patient with synchronous occurrence of concomittant unilateral renal oncocytoma and papillary adenoma, and urothelial carcinoma in bladder. To the best of our knowledge, this is the first case report combining those urinary tumors in the medical literature.

Keywords: *Synchronous, urinary tract, urothelial carcinoma, oncocytoma, papillary adenoma*

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1. Introduction

Urothelial carcinoma is the most common type of bladder cancer (with an incidence over 90%). [1] Papillary adenoma (PA) and oncocytoma are renal epithelial tumors with mostly benign courses. Literature indicates rare case reports on the synchronous occurrence of distinct tumors in the urinary tract. In this study, we present a case of bladder urothelial carcinoma coexisting with renal oncocytoma and PA in the same kidney. Currently, no case report exists in the literature, describing the combination of these three distinct tumors in urinary tract.

2. Case Report

A 69 year-old male was referred to the Urology Clinic with left flank pain. The patient has shown self-limiting painless gross hematuria twice in the last year, but he was not admitted to any medical facility. His medical history was insignificant except for his hematuria anamnesis. Physical examination was unremarkable. Abnormal laboratory findings were detected as following: BUN: 21.2 mg/dL (normal value: 6-20 mg/dl), urea: 50.8 mg/dL (normal value: 16.6-48.5 mg/dL). Creatinine level was normal. The patient was evaluated by non-contrast computed tomography (CT). CT revealed a centrally necrotic lobulated mass of 8x9x10 cm in the inferior pole of the left kidney, and another tumoral mass about 1 cm in diameter was detected in the right inferiolateral wall of the bladder. Transurethral resection (TUR) of bladder tumor and left radical nefrectomy were performed concurrently. The examination of nefrectomy material displayed a well circumscribed, brownish tumoral mass of 10 cm in diameter with a prominent central fibrous scar (Figure 1a). Microscopically, tumor was composed entirely of oncocytic cells with abundant eosinophilic cytoplasm, forming solid groups, nests, trabecular and tubular structures (Figure 1b). Oncocytic tumoral cells lacked cytologic atypia, necrosis or mitotic figures. Immunohistochemically, the tumor cells reacted diffusely for pancytokeratin and EMA. Intense positivity in scattered cells was seen with cytokeratin 7 (Figure 1b-*inset*). There was no immunoreactivity for RCC, vimentin, CD10 and CD117. The tumor was diagnosed as oncocytoma. It was relatively well-circumscribed and did not have infiltrative borders. Besides, PA of 0,2 cm in diameter containing microcalcification was discovered incidentally near the oncocytoma (about 0.2 cm in distance) (Figure 2a). Macroscopically, TUR material was of 4 cc and histopathologic evaluation showed a high grade papillary urothelial carcinoma with lamina propria invasion and the muscularis propria (T2) (Figure 2b). No sign of metastasis was detected in the abdominal CT, thorax CT or cranial CT. The postoperative course was uneventful, and the patient was discharged on third postoperative day. The patient was advised to undergo radical cystectomy for bladder tumor, however he did not attend the follow-up visits. Thus, no further information was obtained regarding the clinical follow-up.

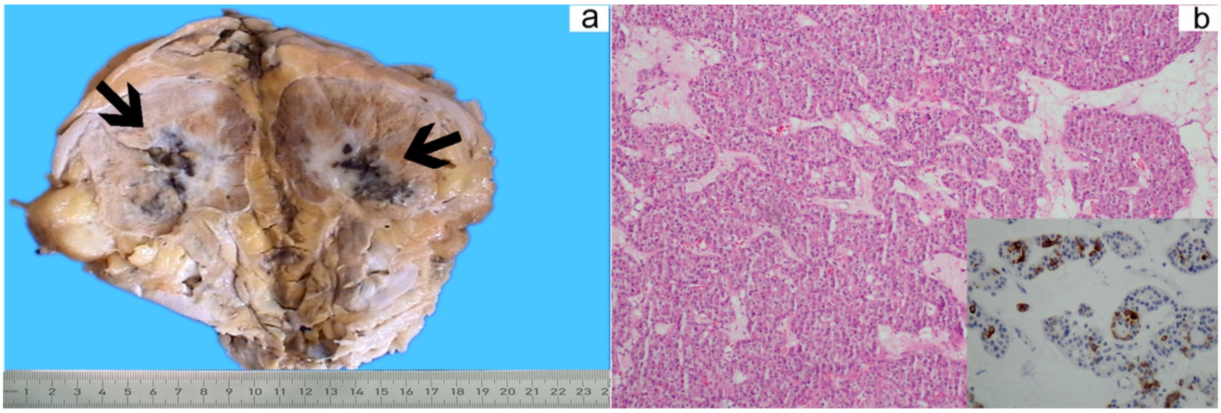

Figure 1. a. The macroscopic photo of the renal oncocytoma with central scar (*arrows*). **b.** Oncocytoma composed of oncocytic cells with abundant eosinophilic cytoplasm forming solid groups and nests (Hematoxylin-eosin stain, x100), *inset*; focal immunopositivity of tumor cells with cytokeratin 7 (Avidin-biotin-peroxidase method, x200)

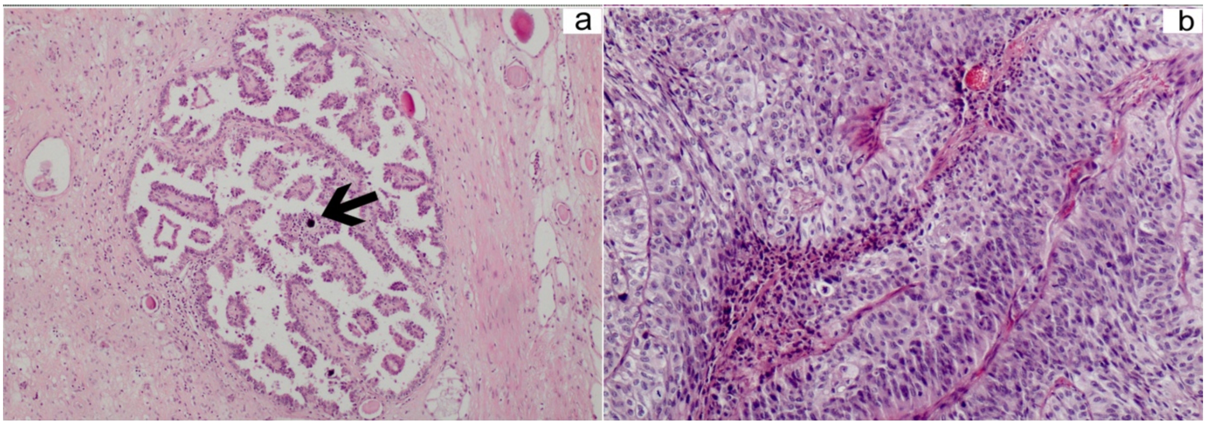

Figure 2. a. Renal papillary adenoma containing calcification (*arrow*) (Hematoxylin-eosin stain, x100). **b.** The photomicrograph of the urothelial carcinoma of the bladder (Hematoxylin-eosin stain, x100)

3. Discussion

Bladder cancer accounts for 3,2% of all cancers. [2] The most common bladder cancer type is urothelial carcinoma. It is encountered more often in men (Male/Female: 3,5/1) and common in the 6th-7th decades. [2] Exposure to tobacco smoke and aromatic amines may be described as one of the most important etiologic risk factors. Cytologic atypia, mitotic activity and structural features are among those factors that define the tumor grades. The present tumor was evaluated as invasive high grade papillary urothelial carcinoma. Renal oncocytoma is an epithelial tumor composed of cells with abundant eosinophilic cytoplasm crowded with numerous mitochondria. [2] Macroscopically, the presence of central fibrous scar is characteristic, as in our case. [2] Oncocytomas usually diffusely stain for AE1/AE3, CAM 5.2, EMA, cytokeratin 14, cytokeratin 20, CD117, E-cadherin and PAX-2 immunohistochemically. [3,4] Focal and intense immunostaining for cytokeratin 7 is regarded as typical for this tumor, and negativity may occur. Oncocytoma is classified as a benign renal tumor in the WHO 2004 classification of renal tumors, and is reported to display nuclear pleomorphism and some mitoses without any indication of malignancy. [2] However, some oncocytomas have been suggested to have malignant potential and show metastases in the literature. [5,6] Nuclear atypia, perinephric invasion, some molecular and genetic features similar to chromophobe renal cell carcinoma (RCC) or oncocytic carcinoma in oncocytoma have been reported to be indicative of malignant behavior in some studies. However, this has not exactly been proved, up to date. [5,6] In addition, the cases reported as metastatic oncocytomas in the literature have been considered as misdiagnoses of probably chromophobe RCC or eosinophilic variant of clear cell RCC, the tumors that enter the differential diagnoses of oncocytoma. [5]

PA is the most common renal neoplasm derived from renal tubular epithelium. [2] The reported incidence in autopsy series is 7-40%. It is characterised by cells with round-oval nuclei occasionally having grooves with absent nucleoli, forming tubular, papillary and tubulopapillary structures similar to type 1 and 2 papillary RCC. [4] It may be accompanied by foamy histiyocytes and psammoma bodies similar to our case. Necrosis and prominent cytologic atypia are the unexpected findings. Incidentally it may be detected as a satellite lesion accompanying RCC. The clinical significance of PA is not clear and the issue is still debated in the literature. Although it is accepted as a benign neoplasm, there are reports suggesting the potentially malignant behaviour of the neoplasm. [2] The approach based on the size of the tumor, the features of papillary morphology and genetic variations are valued currently. It is suggested to accept those tumors smaller than 0,5 cm with low nuclear grade, showing loss of Y chromosome, and presence of trisomy 7 and 17 as PA. [4]

Synchronous multiple tumors of the same or different organs unrelated with a syndrome are rare. It is well known that about 4% of the oncocytomas are synchronous with other tumors in the kidney such as RCC (up to 10%), pelvic urothelial carcinoma and angiomyolipoma. [7,8] In addition, oncocytomas may coexist with extrarenal tumors like prostate, endometrium and ovary carcinoma, and lymphoma. [4,8] Furthermore, as in our case, the association with PA is well recognized. To the best of our knowledge, there has been a case presentation of synchronous bladder urothelial carcinoma and renal oncocytoma, and a case report of synchronous renal oncocytoma, urothelial carcinoma of the bladder and prostatic adenocarcinoma documented in the literature. [9,10] However, no case has so far been reported in the medical literature as our case with synchronous urothelial carcinoma of the bladder, renal oncocytoma and PA of the same kidney. The etiology and pathogenesis of synchronous distinct tumors are still debated. [8,11] Some hypotheses, such as gene mutation, expression of metallothioneins, adjacent tissues being influenced by the same carcinogens, combination of some agents such as nitrosoguanidine and aspirin, or dimethyl-1,2-enzanthracene and cellophane plate, hormonal factors, and similar embryologic origins have been suggested regarding the coexistence of multiple synchronous tumors. [8,11,12] However, none of these hypotheses about the occurrence of synchronous tumors has been proved up to date.

4. Conclusions

The detection of synchronous multiple tumors of the same or different organs is a rare event with obscure etiology and pathogenesis. To the best of our knowledge, the first triple urological tumors including synchronous unilateral renal oncocytoma and PA, and urothelial carcinoma of the bladder have been documented in the present case report.

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