Case Report / Приказ болесника

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Simultaneous ipsilateral rhabdoid renal cell carcinoma and multifocal urothelial carcinoma of the ureter in a patient from the region of Balkan endemic nephropathy – case report and literature review

Симултани ипсилатерални рабдоидни карцином бубрежних ћелија и мултифокални уротелни карцином уретера код болесника из региона Балканске ендемске нефропатије – приказ болесника и преглед литературе

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Симултани ипсилатерални рабдоидни карцином бубрежних ћелија и мултифокални уротелни карцином уретера код болесника из региона Балканске ендемске нефропатије – приказ болесника и преглед литературе

SUMMARY
Introduction Simultaneous ipsilateral coexistence of renal cell carcinoma (RCC) and upper urinary tract urothelial carcinoma (UTUC) rarely occurs. Balkan endemic nephropathy (BEN) is a chronic degenerative tubulointerstitial renal disease, strongly associated with UTUC.

Case outline A 60-year-old man from the region of BEN was referred to our clinic due to right flank pain, fever, and purulent discharge from the cutaneous fistulous opening in the right lumbar area. Multislice computed tomography urography scan showed right-side pyonephrosis and nephrocutaneous fistulous tract between the kidney and the skin in the right lumbar region. Cystoscopy detected papillary tumor protruding from the right ureteric orifice. Right-side nephroureterectomy with bladder cuff excision (BCE) was performed. Histopathological examination revealed rhabdoid RCC of the kidney and multifocal urothelial carcinoma of the ureter.

Conclusion Our case report and literature review indicate that due to rising incidence of multiple primary malignant neoplasms, when treating patients with RCC or UTUC, and especially those from the region of BEN, one should keep in mind the likelihood of synchronous or metachronous occurrence of these tumors.

Keywords: rhabdoid renal cell carcinoma; urothelial carcinoma; Balkan endemic nephropathy; pyonephrosis; nephrocutaneous fistula

INTRODUCTION

Renal cell carcinoma (RCC) represents the most common kidney tumor, accounting for approximately 85% of all kidney malignancies [1]. Although upper urinary tract urothelial carcinoma (UTUC), especially ureteric, occurs more frequently in some regions of Balkan than in other areas in the world, its ipsilateral simultaneous coexistence with RCC is
extremely rare [2, 3]. We report a rare case with simultaneous occurrence of ipsilateral rhabdoid RCC (RRCC) and UTUC of the ureter, in 60-year old man from the region of Balkan endemic nephropathy (BEN).

CASE REPORT

A 60-year old male patient from the region of BEN was admitted to our clinic due to right flank pain and fever up to 39°C. Physical examination revealed a palpable right flank mass, with purulent discharge from the cutaneous fistulous opening localized at the level of the middle axillary line, below the 12th rib (Figure 1).

Laboratory testing revealed elevated inflammatory markers, including white blood cell count of 19.0 × 10⁹ cells/L, with 85.1% neutrophils, C-reactive protein of 58.40 mg/dL, procalcitonin of 16.25 ng/mL and serum creatinine of 1.65 mg/dL. Multislice computed tomography urography revealed normal left kidney and enlarged, nonfunctioning right kidney, with high-density fluid within dilated renal collecting system and a fistulous communication to the skin of the right lumbar region. Cystoscopy detected papillary tumor protruding from the right ureteric orifice.

Following adequate preparation of the patient, right side nephroureterectomy with bladder cuff excision (BCE) was performed. Intraoperative findings showed enlarged right kidney, adherent to surrounding structures due to pyonephrosis, with dilated proximal ureter and a tumor in its distal part. The postoperative course was regular.

On gross inspection, the rhabdoid component of RCC appears as solid white areas at the peripheral part of kidney parenchyma and surrounding fatty tissue. Dominant finding was massive necrosis and hemorrhage. There were a total of three ureteric tumors, all with papillary configuration. One of them was located at the distal part, protruding into the bladder cuff, while the other two had occluded lumen of the upper ureter (Figure 2).

On microscopic examination, with standard haematoxylin and eosin (H&E) stain, the rhabdoid component of RCC was characterized by large round cells with globular
eosinophilic paranuclear inclusion bodies, large eccentric vesicular nuclei with prominent nucleoli. Some cells had clear cytoplasm. The architectural growth pattern was alveolar with delicate fibrovascular septae encircling solid nests of cell. Stroma was scanty, with myxoid change in some part of tumor (Figure 3). The RRCC has been associated with hemorrhage and necrosis with neutrophil infiltration, with vascular and perirenal fat invasion (Fuhrman grade IV, pT3aNxMx). Rhabdoid component was dominant and had been intermixed with sarcomatoid component. RRCC was analyzed using immunohistochemical method with standard En vision system. Rhabdoid cells showed focal immunoreactivity with pancytokeratin and RCC, and vimentin in 100% of tumor cells (Figure 4). Both pancytokeratin and vimentin have given diffuse cytoplasmic staining, with strong accentuation in the globular cytoplasmic inclusion bodies. Despite their morphology, the rhabdoid cells showed no evidence of myoblast differentiation as immunostains for the muscle markers desmin and muscle-specific actin/smooth muscle actin had been negative. Nuclear staining for the Ki-67 nuclear proliferation antigen was strongly present in rhabdoid and sarcomatoid components, in more than 90% of tumor cells. Other investigated immunohistochemical markers, including cytokeratin 7 and 20, were negative in all cells. Ureteric tumors showed classical features of urothelial carcinoma. One of them was high-risk (high-grade; pT2NxMx), while the other two showed classical feature of low-grade, low stage urothelial carcinoma (pTaNxMx) (Figure 5).

DISCUSSION

Simultaneous ipsilateral RCC and UTUC rarely occur. Since the first case presented in the literature as far back as 1921 by Graves and Templeton, approximately 50 cases of simultaneous occurrence of RCC and UTUC in the ipsilateral kidney or ureter, have been reported in the literature until today [3,4]. The incidence of MPMNS ranges from 0.7% to 11.7%, with increasing tendency [5, 6].

In respect to all histologic types of RCC in adults, clear cell is the most common, accounts for 70% of all, while other types are less frequent, including papillary RCC in 10-15%, chromophobe in 4-6%, unclassified in 4-5% and collecting duct carcinoma in less than
UTUCs occur infrequently, accounting for 5-10% of all urothelial carcinomas [7]. However, the incidence is increased in the region of BEN [2,8].

Epidemiological data on simultaneous ipsilateral RCC and UTUC show extremely rare incidence of this phenomenon. In a review of more than 700 cases operated due to RCC, von Eschenbach and coworkers cited only one case (0.14%) of ipsilateral coexistence of RCC and UTUC of renal pelvis [9]. Although the exact mechanism and relationship of ipsilateral RCC and UUT development remains unclear, urinary stone disease, hydronephrosis, chronic irritation and smoking are referred to as the most common etiological factors [10]. The symptoms and demographics in these patients correspond to those that occur in patients with solitary RCC or UTUC, with hematuria as the most common symptom (90%), following by flank pain (19%) and a palpable flank mass (14%) [3, 11]. Compared to the right side, these tumors affect left kidney and ureter three times more often [11]. As proposed by Roupret et al, regardless of tumor location, the standard management in high-risk UTUC includes open radical nephroureterectomy with BCE [12].

Spontaneous kidney to skin fistulous communication is rare condition, occurring as a complication of renal surgery, stone disease, tumors, injuries and perirenal abscess formation [13]. Usually, fistulous tract is directed to the weak anatomical sites of the lumbar region, opening into external space in the area of lumbar (Petit’s) triangle and the superior lumbar (Grynfeltt’s) quadrilateral space [14].

BEN is a chronic degenerative tubulointerstitial renal disease, strongly associated with UTUC, typically occurring in villages of certain areas of the Danube tributaries within the region of the Balkans [8]. The pathology of BEN has been elaborated in several reports. However, one of the hypotheses, namely the chronic poisoning with aristolochic acid (AA), a toxin produced by plants of the Aristolochia, has provided great evidence as to the primary causative agent in BEN, and particularly in the role of developing BEN-associated cancer [15]. The possible cause of BEN development and also the urothelial cancer onset are the DNA adducts since metabolic activation of AAs leads to a reduction of the nitro group to create N-hydroxylaristolactams (N-hydroxyl-ALs) [16]. Recent study by Rosenquist et al has shown that aristolochic acid had been also associated with the occurrence of some tumors other than UTUC, including RCC, bladder tumors, and some liver tumors [17]. Patients with BEN also show a tendency towards certain metabolic alterations, which have not been
observed in patients with other kidney diseases. Petkovic et al showed that the main risk factors for vascular calcification (VC), including systolic blood pressure, as well as serum cholesterol and phosphorus levels, are less pronounced in patients with BEN [18].

In this case study we present a patient with a rare and complex pathological substrate, with an atypical presentation. Interestingly, the existence of RCC was not verified by the diagnostic procedure, since it was hidden by the finding of pyonephrosis, which was a consequence of complete obstruction of the ureter by tumors.

Rhabdoid differentiation in clear cell RCC has a typical pattern of dedifferentiation, suggesting poor prognosis, as reported by Yang et al [19]. Investigating the impact of rhabdoid and sarcomatoid differentiation on prognosis in 264 patients operated due to RCC, Kara et al reported that unlike sarcomatoid, rhabdoid differentiation was not associated with increased risk of lethality [20]. Sarcomatoid differentiation is reported as an independent negative prognostic factor, in both localized and advanced disease, associated with higher grade and stage, with lower cancer-specific survival rates comparing to grade 4 RCC [20].

It is noteworthy to emphasize the possibility of misdiagnosing RRCC for an TCC with sarcomatoid differentiation, which can significantly affect the therapy and prognosis. As for the simultaneous occurrence of RCC and UTUC, it cannot be concluded whether it is a synchronous or metachronous occurrence, due to lack on data when each of these tumors appeared. According to Moertel, a malignant tumor is considered synchronous if it occurs within 6 months of the onset of the previous tumor, while metachronous occurs after that period [21]. Terada et al state that neither the mechanism nor the causal relationship of ipsilateral simultaneous tumorogenesis of RCC and UTUC have been elucidated [22]. Given that the present patient is from the BEN region, one possible explanation is the impact of Aristolochic acid as a mutagenic environmental factor on the genome, and further association with tumorogenesis of various tumors, including UTUC and RCC.

When it comes to follow up, there is no standardized protocol, but postoperative evaluation is performed according to the protocols for UTUC and RCC, separately. At the first postoperative control after 3 months, the patient felt well, with normal findings on urethrocystoscopy, abdominal ultrasound and MSCT of the lungs. To our knowledge, this is the only case report with the simultaneous occurrence of ipsilateral rhabdoid RCC and
multifocal urothelial carcinoma of the ureter, with a clinical presentation in the form of pyonephrosis with spontaneous nephrocutaneous fistula. Having in mind the nature of these tumors, and above all RCC, we consider that in this particular case, rigorous postoperative monitoring is necessary, in order to detect early disease progression and achieve maximum therapeutic effects.

Our case report and literature review indicate that due to rising incidence of MPMNs, when treating patients with RCC or UTUC, and especially those from the region of BEN, one should keep in mind the likelihood of synchronous or metachronous occurrence of these tumors.

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Ethical standards: Written consent to publish all shown material was obtained from the patient.

Conflict of interest: None declared.
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Figure 1. Nephrocutaneous fistula in the right lumbar area
Figure 2. Operative nephroureterectomy specimen showing sites of two mid-ureteric tumors (1, 2) and distal ureteric tumor (3)
Figure 3. Rhabdoid component of renal cell carcinoma with myxoid stromal change (H&E, ×400)
Figure 4. The representative immunohistochemical staining of vimentin in rhabdoid component of renal cell carcinoma (En vision, ×400)
Figure 5. Ureteral associated transitional cell carcinoma (H&E, ×200)