CASE REPORT OLGU SUNUMU

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First Metastasis Site of Multiple Metastatic Renal Cell Cancer: Bladder

Multipl Metastatik Renal Hücreli Kanserin İlk Metastaz Yeri: Mesane

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ABSTRACT We aimed to present a case report of bladder metastasis in a patient with renal cell cancer (RCC), which is a very rare condition. Bladder metastases from RCC are extremely rare. RCC can metastasize through hematogenous, lymphogenous and urinary tract spread. How RCC metastasizes to the bladder is not clearly understood. Dissemination in the urinary tract or also called antegrade pathway is another form of metastasis to the ureter and bladder. This theory was originally proposed after the detection of tumor cells in the urine of patients with RCC. Tumors confined to the bladder mucosa and recurrent urothelial tumors without metastasis are thought to occur in this way. Approximately 20-30% of patients are metastatic at first but isolated bladder metastases of RCC are very rare and usually accompany multiple metastatic disease. In our case, the metastasis was in the bladder for the first time and in isolation.

ÖZET Biz bu vaka sunumunda, oldukça nadir görülen, renal hücre kanserli [renal cell cancer (RCC)] vakada mesanede görülen metastazı sunmayı amaçladık. RCC'den sonra mesane metastazları oldukça nadirdir. RCC hematojen, lenfojen ve üriner sisteme dökülme aracılığıyla metastaz yapabilmektedir. RCC'nin mesaneye nasıl metastaz yaptığı net olarak anlaşılamamıştır. Üriner trakta disseminasyon ya da antegrad yol da denilen yolak üretere ve mesaneye bir diğer metastaz şeklidir. Bu teori esas olarak, RCC'li hastaların idrarında tümör hücrelerinin tespiti sonrası öne sürülmüştür. Mesane mukozasında sınırlı tümörlerin ve metastaz olmaksızın nüks eden ürotelyal tümörlerin bu yolla olduğu düşünülmektedir. Tanı anında yaklaşık %20-30 hasta metastaziktir, ancak RCC'nin izole mesane metastazları çok nadirdir ve genellikle çoklu metastatik hastalığa eşlik eder. Vakamızda metastaz ilk defa ve izole şekilde mesanede görülmüştür.

Keywords: Renal cell cancer; bladder cancer; transurethral resection of bladder; nephrectomy

Renal cell cancer (RCC) is the 6th cancer diagnosed with 5% rate in men and 10th cancer diagnosed with 3% rate in women among all cancers worldwide.[1] The incidence of incidentally detected RCC increases when imaging for non-specific gastrointestinal and musculoskeletal problems in areas where access to imaging methods is easy.[2] Approximately 20-30% of patients are metastatic at first, and progression is observed in 20% of patients after radical surgery. Due to the high recurrence rates, post-treatment follow-up is important. Metastases are most common in the lung (45%), bone (30%), lymph node (28%), liver (20%), adrenal (9%), brain (8%), peritoneum (7%), gastrointestinal tract and pleura (3%). Metastases to other organs are very rare. 61% patients are monometastatic and 39% patients are polymetastatic. Bone and brain metastases often accompany metastases in other regions.[3]

In this publication, we aimed to present a case report of bladder metastasis in a patient with RCC, which is a very rare condition.

CASE REPORT

Informed consent was obtained from our patient regarding this case report.

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A 59 years old patient was diagnosed with left atrophic kidney, grade 4 hydronephrosis and 1.5 cm stone in the left distal ureter after computer tomography (CT) performed 7 years ago in the urology outpatient clinic with complaints of left flank pain. In dimercaptosuccinic acid scintigraphy, the left kidney was reported as a severely hydronephrotic, non-functional. The patient was scheduled for left laparoscopic nephrectomy due to pain. Pathology result after nephrectomy was reported as Grade 3 (Fuhrman grade system), T1bN0, 3.5x3.5x2.5 cm clear cell type RCC and 8 mm diameter papillary type RCC. Lymphovascular invasion and renal capsule invasion were not observed in the tumor. Ureteral surgical margin, vascular surgical margin, pelvis renalis surgical margins are intact. No metastasis was found in the bone scan and thorax-abdomen CT scan performed after the patient had a malignant pathology. In the controls performed in the 1st year, the scans were again clean. At the 18th month in CT, the left ureter was visualized from the mid-section level, and it was noted that from this level, it continued to the ureterovesical (UV) junction as prominently tortuous and dilated. A large stone density of approximately 21x13x25 mm was observed in the UV junction. Transurethral resection of bladder (TUR-B) operation was planned after the cystoscopy was applied to the patient. In the operation, TUR-B was operated the suspicious cancer area protruding from the left orifice to the lumen. The pathology of the lesion originating from the left orifice showed signs of diffuse necrosis and calcification of Von Brunn Islands. It has been reported that there are no findings compatible with malignancy. In the follow-up, the patient had a 10x18 mm solid appearance adjacent to the left ureter orifice, and a heterogeneous solid area of 43x70x59 mm in the left pelvic area was observed in the ultrasonography performed at the 10th month after the TUR-B (RCC recurrence? Intestinal pathology?). After that, oncological positron emission tomography (PET) performed on the patient, multiple hypermetabolic lymphatic nodes are observed (metastasis?) extending to the left external iliac area in the form of a chain starting from the lateral aorta in the L3 vertebral section plane (Figure 1). Thereupon, the patient was scheduled for a re-TUR-B operation. The pathology

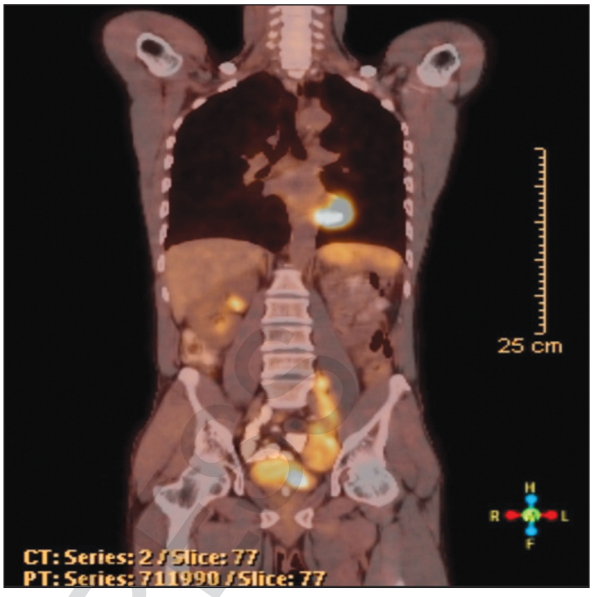

FIGURE 1: Hypermetabolic retroperitoneal lymph nodes and bladder wall thickening on positron emission tomography image.

of the excavated TUR-B from the left side wall was malignant epithelial tumor, the findings were evaluated in favor of clear cell renal cell carcinoma metastasis (Figure 2, Figure 3).

The patient was referred to medical oncology. Interferon treatment was started. However, due to progression, interferon treatment was discontinued and sunitinib treatment was started. Likewise, nivolumab treatment was started due to progression despite sunitinib treatment. However, despite the treatment, progressive disease consistent with metastases in the liver, lung, bones and lymph nodes persists in the latest oncological PET viewed in controls (Figure 4, Figure 5). The patient died exactly 5.5 years after the first diagnosis due to common metastatic disease.

DISCUSSION

RCC can metastasize through hematogenous, lymphogenous and urinary tract spread. How RCC metastasizes to the bladder is not clearly understood. Hematogenous metastasis can occur in 2 ways. The first is through the spread of tumor cells into the systemic circulation. The second is the invasion of tumor cells into the left renal vein and retrograde metastasis to the bladder via the gonadal vein, as described by Abeshouse.[4] In diffuse disease with multiple metasta-

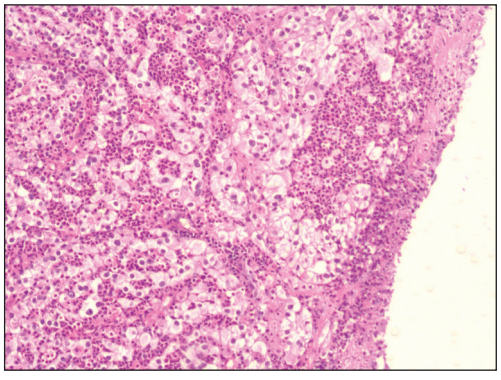

FIGURE 2: Tumor cell proliferation consistent with metastatic renal cell carcinoma forming layers and nests with infiltrating the bladder wall under the ulcerated mucosa (Hemotoxylin & Eosin, x100).

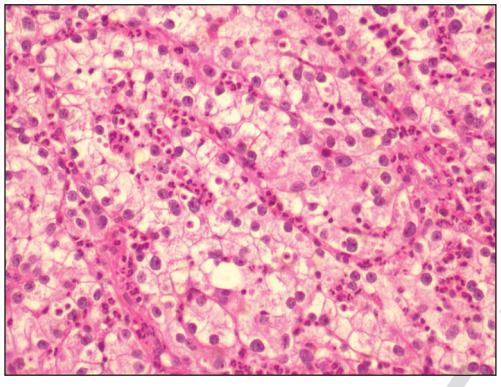

FIGURE 3: Round and polygonal tumor cells with abundant pale eosinophilic and clear cytoplasm, irregular nuclei with prominent nucleoli (Hemotoxylin & Eosin, x200).

tic areas, metastasis is presumed to occur by hematogenous and lymphogenous routes.[5] Dissemination in the urinary tract or also called antegrade pathway is another form of metastasis to the ureter and bladder. This theory was originally proposed after the detection of tumor cells in the urine of patients with RCC.[6] Tumors confined to the bladder mucosa and recurrent urothelial tumors without metastasis are thought to occur in this way.[7]

Bladder metastases from RCC are extremely rare. There are very few case reports in the literature. In the study, in which Matsumoto retrospectively reviewed the case reports, there were a total of 65 patients.[8] In this study, synchronous bladder metastases were detected in 23% of patients and metachronous bladder metastases in 77% of patients. In Saitoh's autopsy series of 1,451 cases involving patients with RCC, a total of 23 (2%) patients had bladder metastases.[9] In the same study, only bladder metastasis was observed in only one patient.

Metachronous bladder metastasis occurred after an average of 33 months after the diagnosis of RCC. While 62% of patients have only bladder metastases, 38% of patients have metastases to other organs in addition to the bladder. RCC pathology was clear cell carcinoma in 92% of patients, and in all cases the pathology of bladder metastasis was consistent with RCC pathology. 2/3 of all patients had superficial (non-muscle invasion) bladder metastases (Ta-T1).

There have been many advances in the treatment of metastatic RCC in the last decade. Systemic treatments are recommended in cases of multiple metastases. While interferon and interleukin-2 acting on cytokines were used before, these drugs were gradually replaced by tyrosine kinase inhibitors and serine-threonine kinase inhibitors (mammalian target of rapamycin-mTOR inhibitors). With the developments in immunotherapy, immune checkpoint inhibitors have also been added to the treatment. Some tyrosine kinase inhibitors (sunitinib, sorafenib, pazopanib) targeting vascular endothelial growth factor and platelet-derived growth factor can be used in targeted therapies.[3]

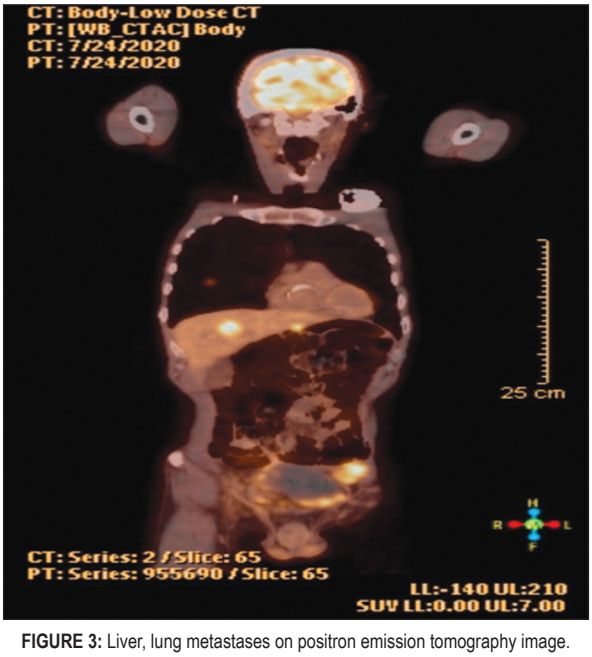

FIGURE 3: Liver, lung metastases on positron emission tomography image.

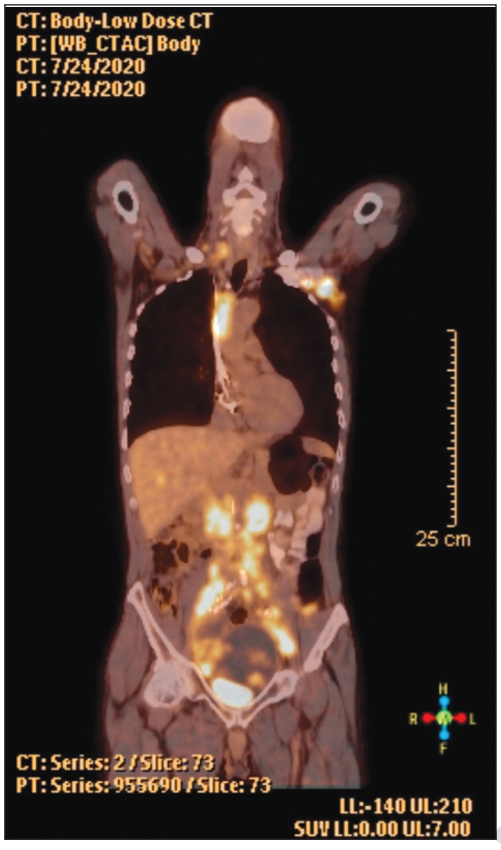

FIGURE 5: Retroperitoneal diffuse hypermetabolic lymph nodes on positron emission tomography image

Although the prognosis of metastatic RCC is poor, metastasectomy has a place in selected cases. For example, resection of lung metastases and local recurrence have a better prognosis than liver and brain metastases.[10] Treatment of RCC metastasis should be specific to each case. Transurethral resection for bladder metastases, partial cystectomy or radical cystectomy for muscle invasive disease may be recommended.[11]

Follow-up after RCC treatment is important. In this way, there is a chance for early intervention about kidney functions, local recurrence, complications, contralateral kidney function and distant metastasis. Although there is no clear consensus on the follow-up scheme after RCC treatment, there are different follow-up schemes for low, intermediate and high-risk diseases. According to the European Association of Urology guidelines, for a patient in the intermediate risk group (T1bN0, fuhrman grade 3) with similar pathology in our patient, it is recommended to check with CT first at the 6th month and then annually.[12]

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Yasin Aktaş;* ***Design:*** *Yasin Aktaş;* ***Control/Supervision:*** *Mahmut Taha Ölçücü;* ***Data Collection and/or Processing:*** *Yasin Aktaş, Mahmut Taha Ölçücü, Döndü Nergiz;* ***Analysis and/or Interpretation:*** *Yasin Aktaş;* ***Literature Review:*** *Yasin Aktaş;* ***Writing the Article:*** *Yasin Aktaş;* ***Critical Review:*** *Mahmut Taha Ölçücü;* ***References and Fundings:*** *Mahmut Taha Ölçücü;* ***Materials:*** *Döndü Nergiz.*

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