Simultaneous metastases of clear cell renal cell carcinoma to the urinary bladder and left retroperitoneal space: A case report and review of the literature

HENGPING LI[1,2], JIANZHONG WANG[2], QIANG WEI[2] and HUAN WANG[3]

[1]Department of Urology, Gansu Province Hospital, Lanzhou, Gansu 730050;
Departments of [2]Urology and [3]Pathology, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, P.R. China

Received December 8, 2014; Accepted December 8, 2015

DOI: 10.3892/ol.2016.4579

Abstract. The present study describes an extremely rare case of simultaneous metastases of clear cell renal cell carcinoma (ccRCC) to the urinary bladder and left retroperitoneal space, occurring subsequent to an open radical nephrectomy. A review of the literature is also considered. A 70-year-old man presenting with diabetes mellitus and hypertension was referred to West China Hospital (Chengdu, China) with constant left flank pain that had been apparent for 2 months. Ultrasonography identified a heterogeneous tumor with a solid component measuring 4.4x3.4x5.0 cm, and computed tomography (CT) revealed a circumscribed and contrast-enhanced tumor in the left kidney. Subsequent pathological analysis of the specimen, obtained from an open radical nephrectomy, confirmed the presence of ccRCC. At 1 month after the radical nephrectomy, an abdominopelvic CT scan identified tumors located on the posterior bladder wall and also in the left retroperitoneal space, forming due to hematuria and acute urinary clot retention. There was no evidence of metastasis to the lungs, bones or other organs. A transurethral resection of the bladder tumor was performed and pathological analysis of the bladder specimen demonstrated metastatic ccRCC. Extensive hydrothorax and general anasarca presented half a month after the transurethral resection, with the patient subsequently succumbing 15 days later.

Introduction

During 2010, renal cell carcinoma (RCC) was estimated to account for 58,240 novel cases of the disease and 13,040 mortalities in the United States, and at present, cases are steadily increasing at a rate of 2.5% per year across population groups (1,2). Clear cell RCC (ccRCC) is one of the most common subtypes of the disease, accounting for 70-80% of all RCC cases (3). A key characteristic of kidney cancer is its tendency to metastasize widely prior to the appearance of any local symptoms or signs (4). In 20-30% of patients with recently diagnosed RCC, radiological evidence of metastases exists at the time of presentation, and 20-40% of patients undergoing a nephrectomy to treat clinically localized RCC will develop metastases (4). The most common locations prone to metastases are the lungs and bones, followed in frequency by the regional lymph nodes, liver, adrenal gland, brain, gall bladder, pancreas and breasts (5,6). Additionally, several studies have reported a number of rare metastatic sites, including the ureteric stump, the ipsilateral and contralateral ureter, and the prostatic fossa (7-9). However, simultaneous metastases of RCC to the urinary bladder and left retroperitoneal space have not yet been reported. To the best of our knowledge, the current study describes the first case of RCC presenting with simultaneous metastases to the urinary bladder and left retroperitoneal space, occurring a short period after a radical nephrectomy.

Correspondence to: Professor Qiang Wei, Department of Urology, West China Hospital, Sichuan University, 37 Guoxue Xiang, Chengdu, Sichuan 610041, P.R. China
E-mail: weiqianglhp@163.com

Key words: renal clear cell cancer, metastatic tumor to bladder, metastatic tumor to retroperitoneal space, bladder tumor, renal tumor

Case report

A 70-year-old man was referred to West China Hospital (Chengdu, China) with chronic left flank pain that had been present for a period of 2 months on December 15, 2014. For the past 10 years, the patient had presented with a history of diabetes mellitus and hypertension. Ultrasonography identified a heterogeneous tumor, comprised of a solid component that measured 4.4x3.4x5.0 cm in size and was located in the upper pole of the left kidney. The echo patterns of the urinary bladder were normal. Abdominopelvic computed tomography (CT) revealed a circumscribed and contrast-enhanced tumor located in the upper pole of the left kidney, and no regional lymphatic metastases, or thrombi of the inferior vena cava and renal vein were identified (Fig. 1A). There was no radiological evidence of metastasis to any other organs or soft tissues. Blood tests and radiographical analysis of the chest were normal. Consequently, an open radical nephrectomy was performed due to compression of the renal hilum by the

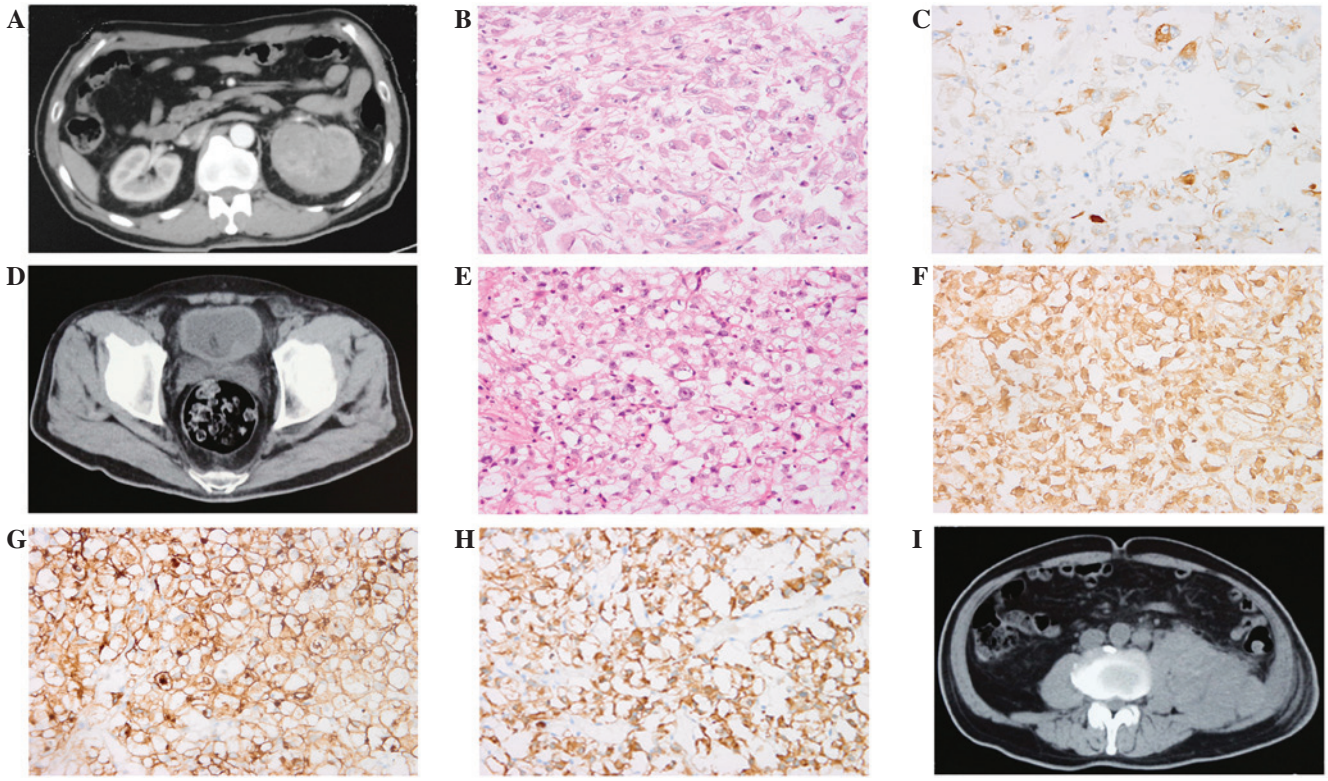

Figure 1. CT of the kidneys, bladder and retroperitoneal space, and immunohistochemical staining analysis of the tumors. (A) Contrast-enhanced CT of primary ccRCC of the left kidney. (B) Staining analysis demonstrating primary ccRCC of the kidney (stain, hematoxylin and eosin). (C) RCC of the kidneys with positive protein kinase C staining. (D) Contrast-enhanced CT demonstrating tumor metastasis to the bladder from the left kidney. (E) Immunohistochemical staining analysis demonstrating RCC metastasis to the bladder, with positive staining for (F) vimentin, (G) cluster of differentiation 10 and (H) cytokeratin 8. (I) Contrast-enhanced CT demonstrating tumor metastasis to the left retroperitoneal space from the left kidney. Magnification, x40. CT, computed tomography; RCC, renal cell carcinoma; ccRCC, clear cell RCC.

larger tumor. On gross examination, the tumor was observed to be compressing the anterior branch of the renal artery and was closely adherent to the surrounding tissue of the pelvis and ureter. Pathological analysis indicated the final diagnosis of ccRCC, which was confirmed as Fuhrman grade IV (Fig. 1B) (10). On microscopic examination, the tumor cells demonstrated a spindled shape that resembled that of sarcoma cells, an abundant, clear cytoplasm, enlarged nuclei with a marked irregular outline and prominently enlarged nucleoli (even at a low magnification), with the addition of bizarre and multilobe nuclei indicating poor differentiation. Necrosis, thick walled vasculature, and neutrophil and lymphocyte infiltration were also observed in the areas of the tumor lesions. Immunohistochemically, the tumor was positive for protein kinase C (Fig. 1C), but negative for RCC and human melanoma mark black 45.

Following radical surgery, neither targeted nor immunological agents were administered on the basis of the RCC treatment guidelines (11). At 1 month after the radical nephrectomy, the patient received transurethral clot evacuation and resection of a sessile tumor (1.0x1.4x1.0 cm) on the left bladder, due to the occurrence of hematuria and acute urinary clot retention (Fig. 1D). Pathological analysis of the bladder tumor indicated the presence of RCC (Fig. 1E). The primary RCC of the kidney (Fig. 1B) presented with features similar to those observed in the metastatic RCC to the bladder (Fig. 1E). The metastatic tumor cells were determined to be positive for vimentin, cluster of differentiation (CD)10, cytokeratin (CK)8 (Fig. 1F-H), CK18 and paired box 2, but were negative for prosaposin, prostate-specific antigen and uroplakin III, indicating a renal origin. An abdominopelvic CT scan also identified a large mass in the left retroperitoneal space (Fig. 1I). There was no evidence of metastasis to the lungs, bones or other organs based on the normal results of relevant CT scans of the bones, abdomen and thorax. Systemic therapy, including chemotherapy and targeted therapy, for the metastatic tumors of the bladder and the left retroperitoneal space, was not administered, primarily due to a weakened performance status (Karnofsky score, <40), anemia and the unstable sugar content of the blood (11). Extensive hydrothorax and general anasarca presented half a month after transurethral resection of the bladder tumor (TURBT). The patient succumbed to the disease 15 days later. The mass in the left retroperitoneal space was considered to have metastasized from the left ccRCC on the basis of the combination of results from the consecutive abdominopelvic enhanced CT and the late metastatic mechanisms of RCC to the bladder and retroperitoneal space. The patient, however, had refused to undergo a fine-needle aspiration biopsy for this mass.

Discussion

RCC is a prevalent malignancy of the kidney that is characterized by the presence of early metastasis (4). Despite the observation of RCC metastasizing to a number of unusual

sites, including the ureteric stump, the ipsilateral and contralateral ureter, and the prostatic fossa (7-9), simultaneous metastases to the urinary bladder and left retroperitoneal space have not yet been reported. Numerous studies have indicated that the average period of time between primary RCC diagnosis and metastasis to the bladder ranges from 2-131 months (11). In the present case, the metastatic masses in the left retroperitoneal space and on the posterior wall of the urinary bladder developed very rapidly, only 1 month after radical nephrectomy. To rule out the possibility of metastases in the bladder and retroperitoneal space prior to the radical nephrectomy, all of the original radiological records were carefully reviewed, with no positive evidence identified to suggest metastases in those sites. Therefore, this suggests that these two sites developed metastases following the first surgery.

The metastatic mechanisms of RCC to the bladder and retroperitoneal space remain unclear. ccRCC is recognized for its propensity to metastasize to unusual sites, and late metastasis, even after ≥10 years, is not uncommon (12). Several studies have proposed a number of possible pathways of hematogenous metastasis occurring through the general circulation and in a retrograde manner, spreading along the paravertebral veins, the testicular/ovarian veins, the intrarenal veins, or by the direct intraluminal transit of tumor cells with seeding in the distal urothelium (12-15). In the present case, rapid metastatic RCC progression was observed in two sites concurrently, namely the urinary bladder and left retroperitoneal space. One of the possible reasons for the occurrence of left RCC metastasis to the left posterior wall of the bladder (near the left orifice of the ureter) is the direct intraluminal transit of tumor cells and/or retrograde metastasis along the left ureter; the current case is in accordance with the outcomes of previous studies (16,17). A possible explanation for the metastasis to the left retroperitoneal space is the retrograde metastasis along the paravertebral, testicular and intrarenal veins; this is in accordance with the abundant, thick-walled vasculature observed pathologically in the primary RCC. Fuhrman nuclear grade is the most commonly utilized histological grading system in RCC (12), and is more effective than any other parameter in predicting the development of distant metastasis following a nephrectomy (10). Additionally, poor differentiation of tumors corresponds with Fuhrman grade IV, and is a very important factor for the prediction of RCC metastasis and survival. Furthermore, an unstable sugar content of the blood and compromised immunological responses may also promote tumor metastasis, and decrease cancer-specificity and over-survival, despite the early stage of the oncology (18,19). In the present case, the unstable sugar content of the blood and a poor diet gave rise to compromised immunological responses with decreased resistance to cancerous metastases. No investigations were performed to assess whether the tumor harbored any notable genetic changes due to the lack of an appropriate control. Additional molecular biological studies may aid the clarification of the potential mechanisms of the rapid metastasis and the unusual metastatic sites of RCC. The aforementioned factors are considered as three important explanations for the rapid metastases typically observed in ccRCC carcinogenesis.

At present, systemic therapy for the treatment of metastatic RCC includes palliative excision and/or use of targeted agents, such as sunitinib, sorafenib and temsirolimus. The therapeutic options available for RCC metastasis to the bladder are a TURBT or a local excision of the bladder. In the present case, TURBT was performed. Considering the weakened performance status of the patient, which includes the symptoms of anemia, an unstable sugar content of the blood and a Karnofsky score of <40, the patient refused systemic treatment or mass exploration in the retroperitoneal space. Subsequently, hydrothorax and general anasarca developed half a month after TURBT, and the patient succumbed to the disease shortly after.

In conclusion, the current study describes an extremely rare case of RCC metastasizing to the bladder and left retroperitoneal space over a short period of time. Despite this case being extremely rare, urologists and oncologists should be aware of the possibility of RCC metastasizing to the urinary bladder and retroperitoneal space in patients at the early stage of the disease, particularly when the patient presents with hematuria and clot retention.

Acknowledgements

This study was funded by the National Natural Science Foundation of China (grant nos. 81200551 and 81270841).

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