Acute Kidney Injury Associated with Renal Cell Carcinoma Complicated by Renal Vein and Inferior Vena Cava Involvement

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Abstract

Acute kidney injury (AKI) is caused by diverse pathologies, although it may occasionally result from concurrent renal efflux disturbances. We herein describe a case of AKI in a patient complicated by renal cell carcinoma (RCC) with renal vein and inferior vena cava (IVC) involvement. A neoplastic thrombus which disrupted the blood flow in the renal vein appeared to play a role in the rapid decline in the renal function. Such a scenario has rarely been mentioned in the previous literature describing the cases of RCC complicated by AKI. Concerns regarding the diagnostic and therapeutic strategies for RCC are also discussed.

Key words: acute kidney injury, hemodialysis, renal cell carcinoma, renal vein obstruction, axitinib


Introduction

Acute kidney injury (AKI) is a common and complex disorder characterized by an abrupt rise in the serum creatinine (sCr) level and/or a significant reduction in the urine output (1). Patients with varying magnitudes of chronic kidney disease (CKD) as well as diabetes, hypertension, and proteinuria have been shown to be at a greater risk of developing the disease (2, 3). A myriad of causes and pathogenic processes, such as vasoconstriction, leukocytosis, vascular congestion, cell death, and abnormal immune and/or growth regulations, can result in AKI (4), although it may occasionally result from concurrent hemodynamic alterations of the renal veins induced by intrinsic involvement of the renal vascular pedicle as well (5, 6). In this report, we describe our experience with one such case of AKI that was severe enough to require renal replacement therapy in a male type 2 diabetic CKD patient. He was complicated by renal cell carcinoma (RCC) with renal vein and inferior vena cava involvement.

Case Report

A 73-year-old male with a history of diabetes, hypertension, and CKD was referred and admitted to our hospital at the end of August 2013 due to AKI. Eleven years previously, he was found to have hypertension and type 2 diabetes with an elevated fasting blood glucose level and hemoglobin A1c (HbA1c) of 10.3%. Thus he had been treated with antihypertensive agents and the subcutaneous injection of insulin, successfully controlling his blood pressure to the ranges of 120-130/60-70 mmHg and HbA1c values at approximately 5.5 to 6.0%. During the last four years prior to this admission, his sCr levels increased gradually, but slowly from 1.13 mg/dL on the end of July 2009 to 1.49 mg/dL at the beginning of May 2013. A steady state urine of 1+ for protein. In the middle of July 2013, he noticed symptoms including progressive swelling of the legs and abdominal fullness when his levels of blood urea nitrogen (BUN)
and sCr were 44 mg/dL and 2.09 mg/dL, respectively. He was administered oral furosemide at a dose of 40 mg/day, which was continued at an increased dose of 140 mg/day combined with fluid restriction. The other only significant findings were slight nausea, a loss of appetite, and easy fatigability appearing at the beginning of August 2013, when he was found to have an elevated sCr level of 3.32 mg/dL. Two weeks later, his manifestations worsened and he became oliguric with a rapid increase in the sCr level of 8.25 mg/dL; thus he was admitted for a further work-up.

At the time of admission, he had gained approximately 7 kg in the previous two months, thereby weighing 62.7 kg. A physical examination revealed severe edema in the lower extremities and abdominal distension. His blood pressure was 125/47 mmHg with a pulse of 42 beats/min, and temperature of 36.1°C. Although the patient’s oxygen saturation was 97% while breathing ambient air, a chest X-ray film demonstrated an accumulation of fluid in the right thorax. There were no rashes or lymphadenopathy, and no petechiae were found. The patient reported that he had been diagnosed to have diabetic retinopathy at a previous hospital. The patient found no petechiae were found. The patient reported that he had been diagnosed to have diabetic retinopathy at a previous hospital. The patient reported that he had been diagnosed to have diabetic retinopathy at a previous hospital. The patient reported that he had been diagnosed to have diabetic retinopathy at a previous hospital.

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Although several neoplasms including RCC, squamous cell carcinoma, Wilms’ tumor, and sarcoma can extend into the renal vein as a neoplasmic thrombus, RCC may be the most frequent cause of malignant renal vein thrombosis (8, 9), while venous vena involve involvement by intraluminal expanding of the neoplasmic tissue has been found in 4-15% of the patients with RCC (8, 10, 11). Regardless of the presence or absence of venous vena involve involvement, the clinical features of renal vein occlusion may depend on the etiology and the response to renal venous hypertension (5). The swiftness of the venous occlusion and development of collaterals could determine the subsequent renal function as well as the clinical manifestations, and thus, the varied spec-

Discussion

Although several neoplasms including RCC, squamous cell carcinoma, Wilms’ tumor, and sarcoma can extend into the renal vein as a neoplasmic thrombus, RCC may be the most frequent cause of malignant renal vein thrombosis (8, 9), while venous vena involve involvement by intraluminal expanding of the neoplasmic tissue has been found in 4-15% of the patients with RCC (8, 10, 11). Regardless of the presence or absence of venous vena involve involvement, the clinical features of renal vein occlusion may depend on the etiology and the response to renal venous hypertension (5). The swiftness of the venous occlusion and development of collaterals could determine the subsequent renal function as well as the clinical manifestations, and thus, the varied spec-
A combination of acute renal vein thrombosis and subsequent AKI with flank pain and/or hematuria has been mentioned previously (12, 13), whereas the neoplastic thrombus from RCC is generally non-obstructive and the sufficient collaterals have developed, thus the majority of RCC patients with renal vein involvement are asymptomatic (8, 11). This may not be surprising since the vena cava at the level of the kidneys can generally be spared from thrombotic processes due to the rapid efflux of blood from the renal vessels (5).

In the current patient, the absence of any contrast enhancement within the right renal vein revealed by the initial CT scan encouraged us to conclude that the blood flow had already been interrupted, thereby leading to the exhaustion of functional clearance in the right kidney. However, the hemodynamic improvement in the left renal vein and concurrent recovery in the renal function after the initiation of axitinib [a potent selective inhibitor of vascular endothelial...
growth factor receptor 1, 2, and 3 which recently received marketing approval as an effective therapeutic for advanced RCC (14, 15)] led us to conclude that the neoplastic thrombus should have disrupted the blood flow in the left renal vein, thereby leading to a rapid and progressive decline in the renal function before the sufficient development of collaterals. Such a scenario has rarely been mentioned in the previous literature describing cases of RCC with renal vein and IVC involvement as well as AKI (8, 10, 11, 16-20); thus, the significance of our experience should be evaluated carefully. We believe that in our case the benefit of radiological imaging using a contrast media outweighed the risk of nephrotoxicity, as is the case in some emergency circumstances (21). Finally, we consider that a filling defect extending to the IVC in the left renal vein should indicate a thromboembolus, resulting from the blockade of the blood flow of the left renal vein by the inhomogeneous mass within the IVC and the right renal vein, a suggestive finding for a tumorous thrombus (22), although the lack of any longitudinal data about the congealing fibrinogenolytic status precludes us from precisely evaluating the nature of such a low-attenuation material. Alternatively, or in addition, the reduced magnitude of the renal blood efflux as well as the renal plasma flow, which should be linked to the pre-existence of CKD with a declined glomerular filtration rate (23-25), might have modulated the intravascular extending behavior, thereby predisposing our patient to the neoplastic tissue-based embolic event that was sufficient to block the blood

Figure 2. Photomicrographs of the renal biopsy specimen. Neoplastic tissue showed findings compatible with clear cell RCC, with an alveolar arrangement (A: Hematoxylin and Eosin staining). Glomeruli with a diffuse accumulation of periodic acid-Schiff (PAS) stain-positive mesangial matrix and rounded acellular mesangial nodules were also noted (B: PAS stain). The scale bar is indicated in each panel.

Figure 3. The time course of the patient. The gradual increases in the daily urine volume were confirmed after the initiation of axitinib treatment. The frequency of HD treatment was reduced to a once-weekly schedule in the middle of October 2013 without any adverse events. Two months later, a twice-weekly HD schedule was commenced to provide a more balanced fluid control.
flow within the left renal vein.

Traditionally, pathological evaluations according to renal biopsies have not been regarded as an appropriate diagnostic procedure for renal masses because the results often did not affect what treatment would be applied and there was a concern regarding tumor-tract seeding (26-29). However, more therapeutic options are currently available that rely on the recent emergence of targeted therapy for advanced RCC (14, 15, 30), and the accurate identification for non-clear cell histology may be required to guide the therapeutic management since patients with such pathologies are more likely to have a decreased survival and less objective responses to the targeted treatments (14, 30, 31). Interestingly, several reports have found no evidence of tract seeding either on microscopic survey or during surgical treatment and advocated expanding the impact of a percutaneous biopsy of renal tumors to obtain prognostic information on patients with metastatic RCC (27, 32), implying the necessity of a consistent evaluation of the potential benefit of the procedure among all subjects with RCC. In this context, our diagnostic policy combined with the renal histological analysis may thus be reasonable. The fact that the majority of the renal biopsy specimens in the current patient were occupied with neoplastic tissue may not be surprising, while such a limited tissue availability precluded us from performing immunofluorescent and electron microscopy, as well as a thorough interstitium evaluation. However, the medical history as well as the morphological characteristics of the kidney shown by light microscopy in our patient encouraged us to ascribe the etiology of CKD to the diabetes and hypertension (33), despite our failure to perform an ophthalmologic evaluation during the observation period.

Currently, no published data regarding the optimal axitinib dosage in patients with advanced CKD are available, and thus, a presumable excessive accumulation may be one of the major concerns of targeted treatment with this agent. Axitinib primarily undergoes hepatic metabolism via the cytochrome P450 (CYP) 3A4 isozyme, with some additional metabolism occurring through oxidation by CYP2C19 and CYP1A2 and glucuronidation via uridine diphosphate glucuronosyltransferase (34). Glucuronide and sulfoxide, major circulating axitinib metabolites, are not active, and less than 1% of the administered agent appears as its unchanged form in the urine (34). Thus, renal elimination should have a marginal importance for the clearance of this agent, and an undue accumulation of axitinib or its metabolites in chronic HD patients may not be of great concern. The validity of our therapeutic strategy using a reduced dose of axitinib is thus unclear in the current patient. Nevertheless, the lack of any pharmacokinetic data from subjects with renal failure severe enough to require renal replacement therapy encouraged us to lower the dosage before toxic events became apparent. We believe that the accumulation of a greater number of similar cases will help to establish appropriate regimens for targeted therapeutic agents, which is a matter requiring both continuous and careful attention.

The authors state that they have no Conflict of Interest (COI).

References


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