Targeted Therapy in Collecting Duct Carcinoma of the Kidney: A Case Report and Literature Review

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Clinical Practice Points

- We reported a patient with locally advanced collecting duct carcinoma (CDC) of the kidney who developed rapid disease progression after multiple rounds of treatment.
- We described current clinical and research progress in understanding and management of CDC.
- We proposed a treatment algorithm in locally advanced and/or metastatic CDC, starting from cytoreduction followed by chemoradiation and targeted therapy.
- We believe integration of genetic mutation screening will help to select appropriate targeted therapies and improve control of the disease over time.

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Introduction

Collecting duct carcinoma (CDC) of the kidney is a rare subtype of renal cell carcinoma (RCC) with distinctive clinical and histopathological features. It represents approximately 2% of all RCCs with < 100 cases reported in the literature. Histologically, CDC is often located at the confluence of the medulla and renal pelvis, and shows a characteristic gray-white-tan color, with absence of foci of necrosis and hemorrhage. It originates in the distal collecting ducts with a tubulopapillary morphology and intracytoplasmic mucicarminophilic material, and most RCCs arise from the proximal tubular epithelium, with a characteristic clear or granular cell appearance in light microscopy.[1] Knowledge of the molecular basis of CDC is still limited. Cytogenetic studies have revealed different chromosomal imbalances between CDC and other types of RCC.[2] Clinically, CDC is characterized by an extremely aggressive phenotype, with a median survival of 11 months and metastasis at presentation in most reported cases. Management of advanced CDC poses a challenge for physicians because > 80% of patients will die within 2 years of diagnosis due to disease progression, despite aggressive local and systemic treatment.[3] We present a case of a man with locally advanced unresectable CDC with a mutation in the neurofibromin 2 (*NF2*) gene in whom conventional chemotherapy had failed but developed a good response to concurrent chemoradiation followed by everolimus maintenance treatment.

Case

A 51-year-old Caucasian man was found to have a right renal mass in computed tomography (CT) scan after he presented with gross hematuria and right flank pain in February 2013. No distant metastasis was identified on further imaging studies. He underwent right radical nephrectomy in May 2013, and was found to have extensive lymph node involvement during the procedure, which was bulky and unresectable. Final pathology showed a pT3aN2M0 high-grade collecting duct tumor, which was 3.5 cm in diameter and extended into the renal vein and fat tissue. He received gemcitabine plus cisplatin beginning in July 2013 as palliative chemotherapy. He had an initial response but developed disease progression in January 2014 after 6 cycles of treatment. He was then started on second-line chemotherapy with docetaxel from March 2014 and his disease progressed during treatment by July 2014. Positron emission tomography (PET)/CT scans showed interval

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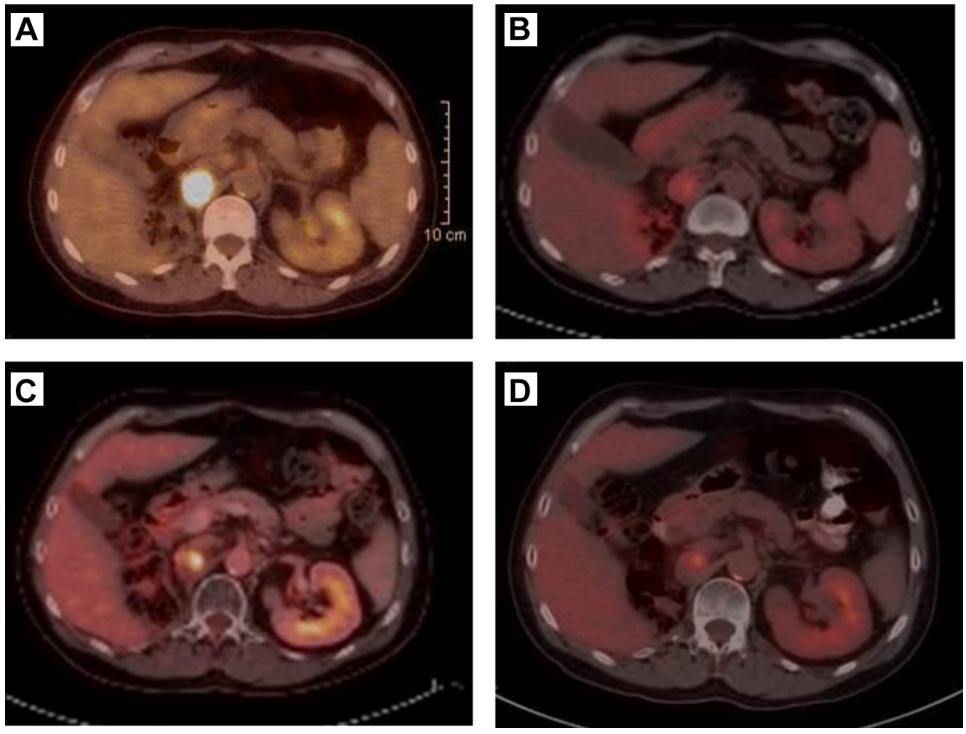
Figure 1 Serial Positron Emission Tomography/Computed Tomograpy Scans Show Changes in a Retroperitoneal Lymphoadenopathy. (A) Before Chemoradiation; (B) After Chemoradiation; and (C and D) Maintenance Everolimus



worsening of the retroperitoneal bulky adenopathy with the largest mass being 6.4 cm, accompanied by inferior vena cava compression (Figure 1A). However, there was no distant metastasis during this interval and his Eastern Cooperative Oncology Group performance status remained at 0 to 1.

He was referred to us for further treatment. Because of the rapid disease progression and impending symptomatic inferior vena cava compression, we started weekly paclitaxel with carboplatin with radiation of 37.5 Gy in 15 fixed doses. We postulated that he would benefit from chemoradiation treatment because his disease was localized and chemoradiation had been used in other urothelial cancers. He finished chemoradiation treatment in November 2014. A restaging PET/CT scan in December 2014 showed a partial response with no new sites of disease (Figure 1B). Further consolidative surgery was explored but was deemed not possible because of high morbidity and potential mortality of the procedure with the extent of the disease. His paraffin tumor block was sent to FoundationOne (Cambridge, Massachusetts) for genomic tests. A single genetic change in the *NF2* gene known as K510fs*4 was detected. This mutation causes a frame shift at codon position 510 where there would normally be a lysine, and results in a stop codon in the new reading frame 4 codon positions downstream from the mutation. On the basis of this result, we started everolimus treatment at 10 mg daily beginning in February 2015. The dose was later decreased to 5 mg daily then to 2.5 mg daily because of anorexia, diffuse ache, and hepatic toxicity. He was maintained with the dose with good tolerance. Repeated PET/CT scans in May 2015 showed an additional response, although modest (Figure 1C), and the most recent PET/CT scan in August 2015 showed further reduced fluorodeoxyglucose activity in retroperitoneal lymph nodes and otherwise stable disease (Figure 1D). He continues to do well with stable disease at the time of this report (9 months of everolimus treatment) and an excellent quality of life.

Discussion

Although substantial improvement has been achieved in the clinical outcomes of clear-cell RCC with immunotherapy and molecular targeted therapy, little progress has been shown in the treatment of CDC. The low incidence of CDC has made further characterization of the disease difficult. Most of the studies have focused on histopathological characteristics of the tumor, and experiences in management of the disease have been sporadically reported in case studies. Valuable prognostic knowledge was obtained from 3 large retrospective studies from the United States,[4] Europe,[5] and Japan,[6] which included 160, 41, and 81 patients, respectively. These studies showed consistently that CDC is male-predominant (70% vs. 76% vs. 72% for the United States, Europe, and Japan studies, respectively), high-grade (70% vs. 78% vs. 99%, respectively), and presents at an advanced stage (38% vs. 81% vs. 57% for $\geq$T3, respectively). Compared with clear-cell RCC, patients with CDC showed significantly worse survival outcomes in the US study. However, the European study showed similar disease-specific