Case Report

Anti-programmed Death Receptor 1 Blockade Induces Clinical Response in a Patient With Metastatic Collecting Duct Carcinoma

Kalen J. Rimar,[1] Joshua J. Meeks,[1] Timothy M. Kuzel[2]

Clinical Practice Points

- Collecting duct carcinoma (CDC) is a very rare subtype of renal cell carcinoma (RCC), accounting for < 2% of all cases of RCC and associated with a very poor prognosis.
- Treatment of metastatic CDC with immunotherapy, chemotherapy, and targeted therapy (vascular endothelial growth factor pathway-targeted agents, mammalian target of rapamycin inhibitors) has shown limited success.
- Programmed death 1 (PD-1) is a receptor expressed by activated T-cells that induces immunosuppression by interaction with PD-1 ligand 1, found on tumor cells.
- Approved PD-1 inhibitors such as nivolumab and pembrolizumab disrupt this immunosuppressive interaction; their use in CDC has not been reported.
- We report the case of a patient with metastatic CDC treated with nivolumab with progression after chemotherapy and tyrosine kinase inhibitor therapy.
- She received 3 mg/kg nivolumab intravenously every 3 weeks for 3 months and underwent repeat imaging; the therapy was well tolerated, without side effects.
- After 3 months of therapy, our patient experienced a partial response of target lesions (46% reduction); the nontarget lesions remained stable, and no new lesions were identified.
- Nivolumab might show antitumor activity in patients with metastatic CDC or non–clear cell RCC in whom standard therapies have failed; further study is encouraged.

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Introduction

Collecting duct carcinoma (CDC) is a very rare subtype of renal cell carcinoma (RCC) that arises from the distal collecting ducts. CDC accounts for < 2% of all cases of RCC and is associated with a very poor prognosis.[1,2] Management of metastatic CDC with immunotherapy, chemotherapy, and targeted therapy (vascular endothelial growth factor pathway-targeted agents, mammalian target of rapamycin [mTOR] inhibitors) has shown limited success.[3,4]

Programmed death 1 (PD-1) is a receptor expressed by activated T-cells. PD-1 ligand 1 (PD-L1) and ligand 2 (PD-L2), found on the surface of tumor cells, stimulate apoptosis of activated T-cells by interaction with the PD1 receptor.[5] PD-1 inhibitors disrupt this immunosuppressive interaction. A recent phase III randomized controlled trial of relapsed clear cell RCC (after antiangiogenic therapy) revealed that nivolumab resulted in significantly longer survival compared with patients who had received everolimus (mTOR inhibitor).[6] These results have laid the groundwork for a paradigm shift in the future management of metastatic clear cell RCC. However, currently, no data are available regarding the use of nivolumab in non–clear cell RCC. We present a case of metastatic CDC that achieved a partial response with compassionate administration of nivolumab.

Case Report

In December 2013, a 53-year-old white woman presented for evaluation of an episode of gross hematuria. She reported a family

[1]Department of Urology
[2]Division of Hematology/Oncology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

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Address for correspondence: Kalen J. Rimar, MD, Department of Urology, Northwestern University Feinberg School of Medicine, 303 East Chicago Avenue, 16-703, Chicago, IL 60611
E-mail contact: K-rimar@northwestern.edu

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history of RCC (father) that had been cured with radical nephrectomy. Her history was also notable for a 15-pack year smoking history and a 50-lb weight loss during the previous 6 months that she attributed to an aggressive diet regimen. She was otherwise asymptomatic. The physical examination findings were unremarkable. Her Eastern Cooperative Oncology Group performance status was 0. The laboratory study results were notable for a hemoglobin of 11.3 g/dL, serum calcium 9.5 mg/dL, lactate dehydrogenase 88 U/L, and glomerular filtration rate > 60 mL/min/1.73 m^2. A triphasic contrast-enhanced computed tomography (CT) examination of the abdomen and pelvis revealed an enhancing mass in the interpolar region of the left kidney (4.6 × 3.1 × 1.6 cm). Also, an adjacent enhancing exophytic renal mass (4.3 × 4.2 × 3.5 cm) was seen. An enlarged left para-aortic lymph node was also noted (1.0 × 1.2 cm), along with additional prominent left para-aortic lymph nodes. Multiple pulmonary nodules at the lung bases prompted a CT evaluation of the chest and a positron emission tomography scan. CT evaluation of the chest revealed > 20 pulmonary nodules, measuring ≤ 7 mm in the long axis. The positron emission tomography scan demonstrated abnormal metabolic activity in 2 left para-aortic lymph nodes, 3 pulmonary nodules, and multiple bony structures, consistent with metastatic disease. Cystoscopy and ureteropyeloscopy revealed benign-appearing urothelium. The results of cytologic evaluation of upper and lower tract washings were negative for malignancy.

An ultrasound-guided biopsy of the left renal lesion was obtained. The core biopsy findings revealed infiltrating malignant cells in discohesive clusters and single cells with scant to moderate cytoplasm, anisonucleosis, nuclear enlargement, irregular nuclear membranes, and dense chromatin. Immunostains for carbonic anhydrase IX, CD10, AMACR, CD117, CK7, P63, and Oct3/4 were negative. Staining for Pax8, cytokeratin 5/6, AE1/AE3 were positive. The final diagnosis was CDC. Samples were sent to Foundation Medicine, Inc. (Cambridge, MA) for detection of genomic alterations, and NF2 R196, EGFR E282K, SETD2 R2399 mutations were identified. Repeat evaluation and renal biopsy at another tertiary referral center were also consistent with CDC. The patient began treatment with cisplatin (70 mg/m^2 on day 1 every 28 days) and gemcitabine (1000 mg/m^2 on days 1, 8, and 15 every 21 days). She completed 6 cycles of chemotherapy, and repeat imaging revealed slightly improved left para-aortic lymphadenopathy and stable left renal lesions. At 4 months after completing chemotherapy, imaging revealed her disease had progressed. She initiated second-line therapy with pazopanib 800 mg daily. At 4 months, she was noted to have stable disease. At 8 months after initiating pazopanib, she had developed a new liver lesion and progression of her left para-aortic lymphadenopathy. Owing to failure of the second-line therapy, the lack of ≥ 3 predictors of short survival, and the rare pathologic findings, she was offered compassionate anti-PD-1 therapy (nivolumab).

Results

Imaging studies 3 months after initiating nivolumab revealed a partial response (46% reduction in the size of target lesions, stable target lesions, and no new lesions) with improvement of her left para-aortic lymphadenopathy (from 2.4 × 1.8 cm to 1.5 × 1.3 cm and from 1.9 × 1.7 cm to 1.2 × 0.7 cm), left mid-pole renal lesion (from 2.9 × 1.5 cm to 1.2 × 0.9 cm), and complete resolution of the hepatic lesion (Figures 1-3). At the last follow-up examination, she was continuing nivolumab, with plans to undergo repeat imaging 3 months later. She tolerated therapy well, with no reported side effects.

Discussion

CDC is a rare subtype of RCC arising from the distal collecting duct. Because of the more advanced stage at presentation and the lack of effective systemic therapy, most patients will die within the first 3 years of diagnosis.[1,2] Although radical nephrectomy remains the mainstay of management for localized disease, regardless of the subtype, the management of metastatic CDC has not been clearly defined. This ambiguity in management is also true for all types of metastatic non—clear cell RCC, because most studies of systemic therapy included patients with predominantly clear cell histologic features.[7] The rarity of CDC has made it difficult to extrapolate data from studies of systemic therapy for non—clear cell RCC, because they often exclude or did not contain patients with this particular histologic subtype.

Figure 1 Computed Tomography Scan of Abdomen and Pelvis Demonstrating Renal Lesion (Arrow) Before (Left) and After (Right) Treatment With Nivolumab