Renal Collision Tumor Composed of Clear Cell Carcinoma and Collecting Duct Carcinoma Treated with Nivolumab and Ipilimumab: Case Report and Literature Review

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CASE REPORT

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ABSTRACT

Introduction and importance: Collision tumors refer to the phenomenon where two or more different and unrelated tumors occur in the same location of an organ and form a single lesion. We present the first case of renal collision tumors composed of clear cell carcinoma (ccRCC) and collecting duct carcinoma (CDC) treated with combined therapy of nivolumab and ipilimumab.

Case presentation: An 89-year-old male presented to the emergency room with back pain. Imaging studies demonstrated a large tumor in the left kidney with renal vein thrombosis. After radical nephrectomy, the histopathological report showed collision tumors with ccRCC and CDC components. The patient was included in a treatment protocol based on nivolumab (220 mg) and ipilimumab (73 mg) every 21 days, however, obtaining no clinical responses after 5 cycles of treatments.

Clinical Discussion: Immune checkpoint inhibitors have become a new standard of care for patients with advanced ccRCC. However, current literatures showed inconclusive evidence on the efficacy of immune checkpoint inhibitor for metastatic CDC. As collision tumors with ccRCC and CDC components were infrequently reported in the literature, we also discuss the histological and immunohistochemical findings, clinical outcomes, and a literature review on this type of renal collision tumors.

Conclusion: CDC is a rare and highly aggressive type of renal neoplasms, with limited treatment choices. More studies are needed to evaluate the efficacy of immune checkpoint inhibitors on CDC and its associated collision tumors.

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Highlights:

- Collecting duct carcinoma is a rare and highly aggressive type of renal neoplasms, with a poor clinical outcome.
- Radical nephrectomy alone is rarely curative.
- The use of immune checkpoint inhibitors for collecting duct carcinoma needs further evaluation.
- The use of HMWCK as a histologic marker for differential diagnosis of collecting duct carcinoma may need to be evaluated.

INTRODUCTION

Collision tumors refer to the phenomenon where two or more different and unrelated tumors occur in the same location of an organ and form a single lesion. We present the first case of renal collision tumors composed of clear cell carcinoma (ccRCC) and collecting duct carcinoma (CDC) treated with combined therapy of nivolumab and ipilimumab. In addition, we discuss the histological and immunohistochemical findings, clinical outcomes, and a literature review on other renal collision tumors. This case report has been reported in line with the SCARE Criteria [1].

CLINICAL CASE

An 89-year-old male presented to the emergency room with back pain. The patient's medical history was

significant for diabetes mellitus, asthma and dyslipidemia. Drug history and family history are unremarkable. Computed tomography (CT) demonstrated a large tumor in the left kidney with renal vein thrombosis (**Figure 1**). There was also evidence of multiple retroperitoneal lymph nodes involvement. The patient underwent uncomplicated left radical nephrectomy.

The nephrectomy specimen showed a 6 cm × 4 cm × 4 cm tumor in the middle pole of the kidney. On histologic examination of the lesion (**Figure 2**), two distinct morphologies were seen. On low power, there was a well-demarcated border between the two tumors. One tumor had irregularly shaped glands with a thin fibrovascular stroma containing small blood vessels, whereas the second sat in a more abundant desmoplastic stroma. On high power, the first tumor showed abundant clear cytoplasm with minimal atypia and only occasional small nucleoli (World Health Organisation(WHO) grade 1), whereas the second tumor had frankly malignant

Figure 1 Axial image of Contrast enhanced CT demonstrating an exophytic hypodense lesion in the left kidney with some fat stranding around it. Later phases did not demonstrate any filling defect in the renal calyces (not shown).

Figure 2 Histologic appearance of the tumors. H&E. Panels (A) and (B) (original magnification 2× and 4×, respectively) with ccRCC on the top and collecting duct carcinoma on the bottom. Panels of ccRCC (C) and collecting duct carcinoma (D) at original magnification 10×.

cytology (WHO grade 3). On immunostaining (**Figure 3**, **Table 1**), both tumors stained with carbonic anhydrase IX (CAIX), consistent with renal origin, but only the ccRCC component showed diffuse reactivity with CD10 while the collecting duct carcinoma was strongly positive for CK7 and extremely weak, mainly luminal reactivity for high molecular weight keratin (HMWCK) and CD10.

Two months after the initial nephrectomy, multiple liver and lung metastases, plus right-sided lymph nodes involvement, were discovered on a follow-up CT. According to Heng risk criteria, the patient belonged to the poor risk group. The patient then underwent combination immunotherapy with nivolumab (220 mg) and ipilimumab (73 mg) every 21 days.

After 5 cycles of treatment, a follow-up CT showed disease progression thus treatment was discontinued. The patient opted for palliative care and succumbed to his disease 6 months following diagnosis.

DISCUSSION

Collision tumors in the kidney are rare. To date, there have been 9 reports, including our report, presenting 10 cases of collision tumors composed of ccRCC and CDC (**Table 2**) [2–9]. Of these 10 patients, 9 were male. These

patients were aged from 21 to 89, with a median age of 55.5 years, which was lower than the median age (64 years) of patients with RCC in general [10]. Laterality was equal, with five tumors occurring on each side. Lung was the most common place where metastases were found (50%), followed by lymph nodes (40%), bone (30%, including one spinal metastasis), liver (20%), bladder (10%), inferior vena cava (10%) and psoas muscle (10%). All patients underwent radical nephrectomy. Adjuvant chemotherapy was used on 2 patients [4, 6]. One patient had combined therapy of cabozantinib and nivolumab [3]. One patient was treated with radiotherapy and adjuvant sunitinib [8]. Survival among these patients varied, from 6 weeks after nephrectomy to no sign of disease progression 12 months after nephrectomy.

In recent years, immune checkpoint inhibitors have become a new standard of care for patients with advanced ccRCC. In particular, a phase III clinical trial demonstrated that a first line combined therapy of nivolumab and ipilimumab significantly prolonged survival in patients with intermediate or poor risk ccRCC, compared to sunitinib [11].

While the treatment protocol for ccRCC has been well established, treatment choices for CDC are limited. CDC is a rare and highly aggressive type of renal neoplasms, with a mean survival of 11 months [12]. A systematic

Figure 3 Immunostains of the tumors, with ccRCC on the top and collecting duct carcinoma on the bottom, original magnification 10×. (A) CAIX, (B) CD10, (C) CK7, and (D) CK903.

ANTIGEN/ ANTIBODY	CLONE	MANUFACTURER	DILUTION	CCRCC PATTERN (PRESENT CASE)	CDC PATTERN (PRESENT CASE)
CA-IX	MRQ-54 (M75)	Cell Marque, California	1 : 100	Diffuse, strong	Diffuse strong
CD10	56C6	Novocastra, Leica BioSystems, Germany	1 : 50	Diffuse, strong	Patchy, very weak, luminal
CK7	OV-TL 12/30	Dako, Denmark	1 : 50	Patchy, weak	Diffuse, strong
CK903 (HMWK)	34E12	Dako, Denmark	1 : 50	Negative	Very weak, luminal
GATA3	L50-823	Cell Marque, California	1 : 200	Negative	Negative
P63			1 : 50	Negative	Negative
PSA	35H9	Leica BioSystems, Germany	Predilute	Negative	Negative

Table 1 Antibodies Used at Soroka University Medical Center.

STUDY AND YEAR OF PUBLICATION	AGE (YEARS)/SEX	CLINICAL PRESENTATIONS	LOCATION OF CCRCC	LOCATION OF CDC	DIMENSION(CM)	METASTASES	TREATMENT(S)	SURVIVAL	NOTE
Salazar-Mejia et al., 2020	47/M	Persistent dry cough, weight loss	Left	Left	16 as a single mass	Lung metastases, adrenal involvement and regional adenopathy before nephrectomy	Left Radical Nephrectomy, followed by combined therapy of cabozantinib and nivolumab; switched to nivolumab only 10 months after combined treatment	15 months after initial diagnosis	
Yavuzsan et al., 2018 (1)	54/M	Right flank pain	Right upper pole	Right upper pole	7 as a single mass	Para-aortic lymph nodes involvement and lung metastasis before nephrectomy	Right Radical Nephrectomy	6 weeks after surgery	
Yavuzsan et al., 2018 (2)	62/M	No presentation, discovered in routine checkups	Right middle pole	Right middle pole	5 as a single mass	No	Right Radical Nephrectomy	No signs of metastases for 10 months after surgery	
Burch-Smith et al., 2014	67/F	Back and abdominal pain, urinary frequency	Left upper pole	Left upper pole	6 as a single mass	Lung metastases (CDC component) at 5 months post-nephrectomy; soft tissue and bone metastasis in thoracic spine	Left Radical Nephrectomy; paclitaxel and carboplatin after lung metastasis was discovered; switched to doxorubicin and gemcitabine after neuropathy was developed	14 months after initial diagnosis	
Hennessey et al., 2013	21/M	Back pain	Left lower pole	Left lower pole	10.3 as a single mass	Spinal metastases (CDC component) and retroperitoneal nodes involvement before nephrectomy	Left Radical Nephrectomy; urgent radiotherapy for progression of spinal metastases; adjuvant sunitinib	8 months after surgery	
Tsai et al., 2009	57/M	Acute pyelonephritis	Right	Right	Not provided	Lung and bladder metastases (RCC component) 1-month post-nephrectomy; Multiple metastases to the liver, inferior vena cava and psoas muscle occurred	Right Radical Nephrectomy followed by adjuvant chemotherapy; transurethral resection of the bladder after bladder metastases were discovered	3 months after initial diagnosis	Coexistence of urothelial carcinoma of renal pelvis

(Contd.)

STUDY AND YEAR OF PUBLICATION	AGE (YEARS)/SEX	CLINICAL PRESENTATIONS	LOCATION OF CCRCC	LOCATION OF CDC	DIMENSION(CM)	METASTASES	TREATMENT(S)	SURVIVAL	NOTE
Cho et al., 2004	24/M	Left abdominal mass	Left inner nodule	Left outer nodule	1.5 for ccRCC; 14 for CDC	No	Left Radical Nephrectomy	No signs of metastases for 12 months after surgery	Nodule to nodule pattern
Nagamoto., 2001	51/M	Gross hematuria	Right	Right	Not provided	Not provided	Right Radical Nephrectomy	Not provided	Coexistence of multiple renal cysts
Auguet et al., 2000	73/M	Microscopic hematuria	Right upper pole	Right lower pole	1.3 for ccRCC; 6 for CDC	Bone metastases at 8 months post-nephrectomy	Right Radical Nephrectomy	Not provided	
Our case	89/M	Back pain	Left middle pole	Left middle pole	6 as a single mass	Retroperitoneal lymph nodes involvement before nephrectomy; lung, liver metastases and paraaortic involvement 2 months post nephrectomy	Left Radical Nephrectomy, followed by combined therapy of nivolumab and ipilimumab		

Table 2 Summary of Clinicopathologic Findings in Reported Cases of Collision Tumors composed of ccRCC and CDC.

review suggested that gemcitabine and cisplatin should be considered as the standard treatment of metastatic CDC [12]. The benefit of cytoreductive nephrectomy in patients with metastatic CDC is unclear [12].

Evidence supporting the use of immune checkpoint inhibitors in patients with CDC is scarce. To date, three case reports have documented a clinical response with nivolumab monotherapy in patients with metastatic CDC [13–15]. In a retrospective study, four patients with CDC were treated with nivolumab. Only one patient achieved partial response, while others had progressive disease [16]. With respect to combined therapy, there is one case report presenting a complete response with nivolumab and ipilimumab in a patient with metastatic CDC after radical nephrectomy [17]. In our case, the patient did not show a clinical response to combined therapy of nivolumab and ipilimumab. More studies should be conducted to evaluate the efficacy and criteria of using immune checkpoint inhibitors against CDC.

The diagnosis of CDC relies heavily on histological study, according to WHO's classification of urological tumors [18]. Immunohistochemical staining can be useful in the differential diagnosis of CDC. In our case, CDC was strongly positive for CK7 and extremely weak, mainly luminal reactivity for HMWCK. Skinnider et al. suggested that expression of HMWCK could help differentiate CDC from tubulocystic carcinoma and renal medullary carcinoma [19]. Nonetheless, recent studies with larger sample sizes showed only 26–29% of CDCs were immunoreactive with HMWCK [20, 21]. In addition, Gupta et al showed CDC and renal medullary carcinoma expressed HMWCK in a similar rate [21]. More studies are needed to clarify its sensitivity in the differential diagnosis of CDC.

CONCLUSION

In this report, we presented the first documented case of collision tumors composed of ccRCC and CDC, which was treated with combined therapy with nivolumab and ipilimumab, despite no clinical response. Treatment choices for CDC are limited. More studies are needed to evaluate the efficacy of immune checkpoint inhibitors on CDC and its associated collision tumors.

ABBREVIATIONS

ccRCC, clear cell renal cell carcinoma; CDC, collecting duct carcinoma; CT, computed tomography; HMWCK, High molecular weight cytokeratin; WHO, World Health Organisation.

ETHICS AND CONSENT

Written informed consent was obtained from the patient

for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief on request.

COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

CS: Investigation, Data Curation, Writing – Original Draft; **MK:** Investigation, Data Curation, Writing – Original Draft; **WK:** Investigation, Resources, Writing – Review & Editing, Supervision; **GB:** Resources, Writing – Review & Editing, Visualization; **BS:** Conceptualization, Investigation, Resources, Writing – Review & Editing, Visualization, Supervision; **OL:** Investigation, Resources; **MZ:** Resources, Writing – Review & Editing; **SAS:** Resources, Writing – Review & Editing; **EM:** Resources, Writing – Review & Editing; **DL:** Resources, Writing – Review & Editing.

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