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Therapeutic Challenges in the Management of Collecting Duct Carcinoma of the Kidney: A Case Report with Review of Literature

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Abstract

Collecting duct carcinoma (CDC) of the kidney is a rare type of renal cell carcinoma. It is an aggressive tumor with a poor prognosis and limited treatment options. A 67-year-old man, during evaluation for hematuria, loss of appetite and weight loss, and flank pain, was found to have a left renal mass with lung and bone metastasis. He underwent a left radical nephrectomy, and histopathological examination confirmed CDC. He received palliative chemotherapy with carboplatin and gemcitabine. Computed tomography (CT) scan after three cycles showed partial response. Chemotherapy was stopped due to worsening renal function after five cycles. Immunohistochemical studies done for programmed cell death ligand 1(PDL1) SP263 and Her2 neu were negative. Next-generation sequencing for 75 therapeutically actionable gene panels showed loss of function mutation in the neurofibromatosis type 1 (NF1) gene. Missense mutations involving Platelet derived growth factor receptor alpha gene (PDGFRA), FAT atypical cadherin 1 (FAT1), and Androgen receptor (AR) genes were reported as variants of unknown significance. No clinically relevant alterations were detected in liquid biopsy. Consequently, he was started on sunitinib. After 2 months, he developed brain metastasis and was treated with whole brain radiation therapy. Systemic therapy was changed to single-agent Nab-paclitaxel. After three cycles, he developed a cutaneous metastasis in the forearm and chemotherapy was changed to single-agent doxorubicin. After three cycles of doxorubicin, he succumbed to the disease. He survived for 16 months after diagnosis. The first-line treatment for metastatic CDC is chemotherapy with gemcitabine and cisplatin. There is no established second-line treatment. In this era, next-generation sequencing for targetable genetic alterations can help us select the treatment for subsequent lines of therapy.

Keywords
- case report
- collecting duct carcinoma
- immunotherapy
- next-generation sequencing
- targeted therapy

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Introduction

It was Fleming and Lewi in 1986 who described collecting duct carcinoma (CDC) as a type of renal cell carcinoma (RCC).[1] It accounts for less than 1% of all RCCs. Usually, it presents with hematuria, backache, and mass per abdomen. Diagnosis is by computed tomography (CT), which shows a renal mass involving the medulla, and tissue biopsy. In localized disease, the treatment of choice is nephrectomy and adjuvant chemotherapy with cisplatin and gemcitabine. In metastatic disease, the first-line treatment is palliative chemotherapy with gemcitabine and cisplatin/carboplatin. Patients not fit for cisplatin can be offered carboplatin with gemcitabine. There are no standard second-line treatment options. We have less experience with immunotherapy, and results do not seem to have improved. Experts all over the world suggest molecular studies in such rare cases. Studies with next-generation sequencing (NGS) will give insight into common molecular alterations, and targeting them can benefit the patients. There are very few studies on molecular alterations. Here, we present a rare case of metastatic CDC of the kidney. In our case, we have done NGS and the results will add to the scientific literature and will help pave the way for further treatment options for this rare variant of RCC.

Case Report

A 67-year-old gentleman presented in April 2023 to a multispecialty hospital with a history of hematuria for 5 months, loss of appetite and weight for 3 months, and flank pain for 1 week. He had a past history of diabetes mellitus and coronary artery disease on regular medications. He was evaluated with an ultrasound of the abdomen and pelvis, which showed a left renal mass of a size of 4×4 cm. A contrast-enhanced CT of the kidney, ureter, and bladder revealed a mass measuring $5.1 \times 3.3 \times 4.1$ cm in the upper pole of the left kidney with perinephric fat stranding, left renal hilar and paraaortic lymphadenopathy, and suspected bilateral lung metastasis (9×7 mm). He underwent left open radical nephrectomy. The histopathology report showed a high-grade tumor with tubular and tubulopapillary patterns of size 5 cm involving the upper pole of the left kidney. The tumor extended into the capsule and infiltrated the renal sinuses and renal parenchyma, not invading the adrenal gland, perinephric fat, ureter, or renal vessels. There was 10% necrosis without sarcomatoid or rhabdoid features or lymphovascular invasion. Three out of nine hilar lymph nodes showed tumor metastasis that was histomorphologically suggestive of CDC. He was referred to us for further management. His symptoms at presentation in our outpatient department (OPD) were loss of appetite and fatigue. His Eastern Cooperative Oncology Group (ECOG) performance status was 1, pallor was present, and a well-healed surgical scar was observed in the left subcostal region.

On evaluation, his hemoglobin was 10 g/dL, creatinine was 1.7 mg/dL, urea was 30 mg/dL, and creatinine clearance was 45 mL/min. Other blood investigations were within normal limits. Fluorine-18 fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET CT; ►**Fig. 1**) revealed ^{18}F-FDG–avid multiple bilateral lung and pleural metastasis, right hilar and bilateral pulmonary ligament lymph nodes, and ^{18}F-FDG-avid lytic sclerotic skeletal metastasis (right scapula, cervicodorsal vertebra, left 8th rib, and bilateral iliac bone). The specimen, slides, and blocks were reviewed by an expert pathologist from our center and the diagnosis of CDC was confirmed (►**Fig. 1**). Immunohistochemistry was not performed as the histopathology was concordant with CDC. He received palliative chemotherapy with carboplatin AUC5 intravenous infusion in 500 mL normal saline over 30 minutes and gemcitabine 1,000 mg/m^2 in 250 mL normal saline over 30 minutes. Cisplatin was deferred, and carboplatin was given in view of reduced creatinine clearance. Noncontrast CT scan after three cycles showed partial response. Chemotherapy was tolerated well, but the patient developed worsening renal function (creatinine 2.4) and oliguria after five cycles, which improved on conservative management and further chemotherapy was stopped. Immunohistochemical studies were done for programmed cell death ligand 1 (PDL1; VENTANA PD-L1 SP263 Assay; Roche Holdings AG, Basel, Switzerland), which showed a tumor proportion score of 0% and Her2 neu was negative (score 0). Custom-targeted hybrid-capture-based NGS assay for 75 therapeutically actionable gene panels showed loss of function mutation in the neurofibromatosis type 1 gene (variant allele frequency [VAF]: 14.32%). There were missense mutations involving the PDGFRA (VAF: 21.79%), FAT1 (VAF: 39.36%), and AR (VAF: 11.02%) genes, which were reported as variants of unknown significance. As the sample quality was very low, it was advised to repeat the test from a fresh biopsy sample to identify the copy number variations. Biopsy from the lung and bone was not feasible. Hence, the molecular pathologist suggested proceeding with liquid biopsy to find out targetable alterations. A liquid biopsy (50 gene panels) using Genexus Next Generation Sequencer was done and no relevant alterations were detected. Food and Drug Administration (FDA) approved NGS could not be done because of logistic and financial reasons. After discussing with the molecular tumor board, it was decided to start him on tablet sunitinib 37.5 mg once daily —2 week on and 1 week off schedule. The patient tolerated sunitinib well. After 2 months, he presented with severe headache, which was evaluated with ^{18}F-FDG PET CT, which revealed new multiple hypermetabolic brain lesions, and stable extracranial disease. He received palliative whole brain radiation therapy to a dose of 20 Gy in five fractions. He was continued on sunitinib but developed multiple episodes of hemoptysis after a week, which was settled with conservative management. Immunotherapy was not offered given PDLI tumor proportion score (TPS) of 0% and microsatellite stability on NGS. Systemic therapy was changed to single-agent Nab-paclitaxel 125 mg/m^2 intravenously on day 1, day 8, and day 15 every 28 days. He developed grade 3 anemia (hemoglobin 6.2 g/dL), which was managed with packed red blood cells (PRBC) transfusion. After three cycles, he developed a cutaneous nodule in the left arm. A fine needle aspiration cytology (FNAC) confirmed malignancy correlating with primary

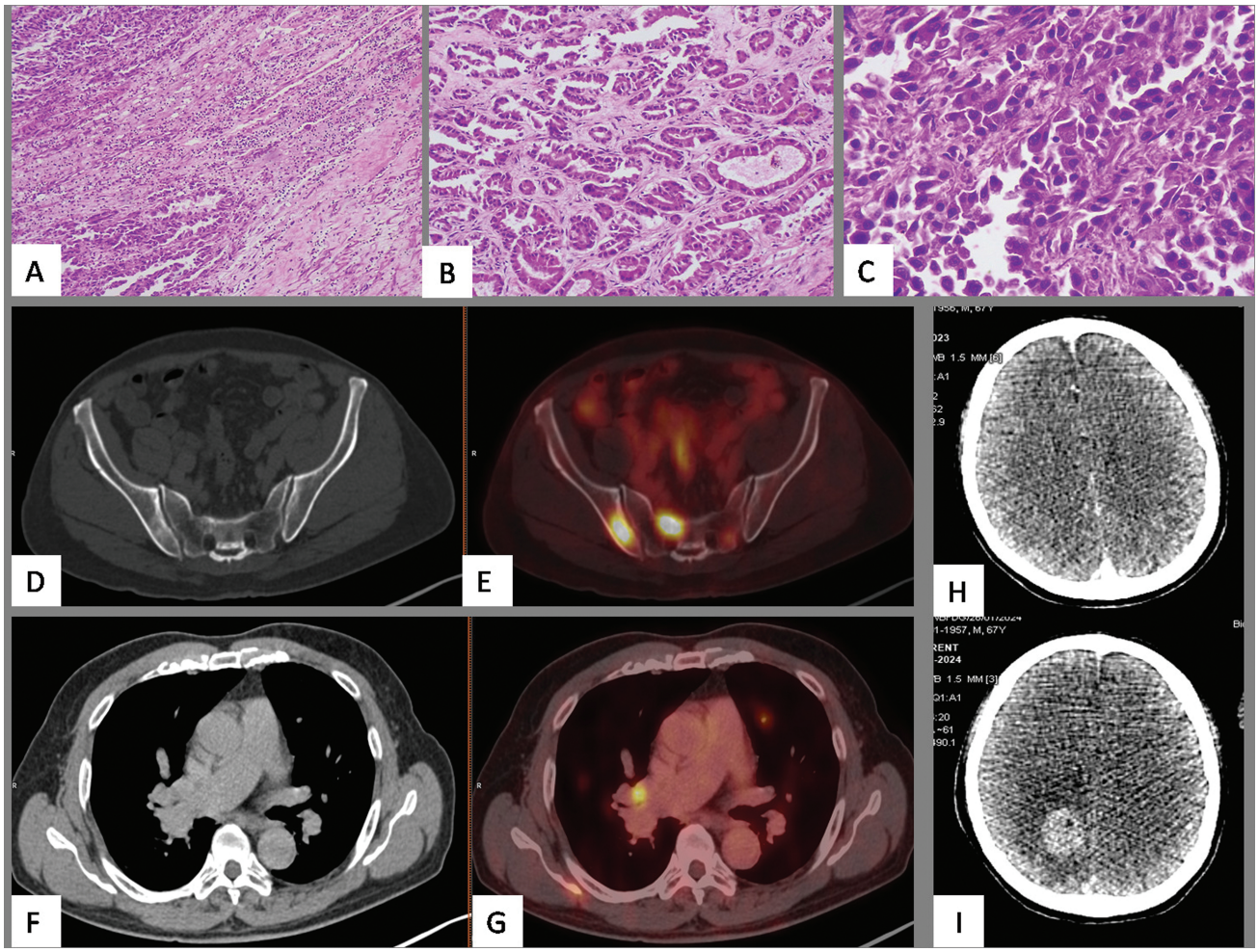

Fig. 1 (**A**) Histopathological features of collecting duct carcinoma: desmoplastic stroma. (**B**) Tubular pattern with cystic spaces. (**C**) Abundant cytoplasm. (**D**) Computed tomography (CT) image showing sclerotic metastasis in the iliac bone. (**E**) Fluorodeoxyglucose (FDG) positron emission tomography (PET) CT image showing FDG uptake in the iliac bone. (**F**) CT image showing hilar lymphadenopathy and lung nodule. (**G**) FDG PET CT image showing FDG uptake in the hilar nodes lung nodule. (**H**) CT image after chemotherapy with gemcitabine and carboplatin, which shows normal brain parenchyma. (**I**) CT image showing new brain lesion after 2 months of sunitinib.

malignancy in the kidney. Noncontrast CT of the thorax and abdomen revealed stable disease. In view of clinical progression, chemotherapy was changed to single-agent doxorubicin 60 mg/m^2 IV push every 3 weeks with erythropoietin support. He received the third cycle in July 2024 without much toxicity. He developed a urinary tract infection after a week, which was managed with antibiotics. In August 2024, he developed dyspnea and succumbed to his illness. He survived for 16 months after diagnosis.

Discussion

CDC of the kidney arises from the Bellini duct, RCC from the convoluted tubule, and urothelial carcinoma from transitional cells of the bladder. In 1976, Mancilla-Jimenez et al reported the first case wherein atypical and hyperplastic changes were seen adjacent to the collecting duct epithelium in 8% of cases of RCC.[2]

Based on histology, renal cancers can be divided into clear cell (75%) and nonclear cell types (25%). Types of nonclear cell carcinomas are papillary (10%), chromophobe (5%), cystic solid (1–4%), collecting duct (1%), and medullary (1%); other rarer types are Xp11 translocation, mucinous tubular, and spindle cells.[3] CDC is a nonclear cell type, constituting less than 1% of RCC. It has a male preponderance in the ratio of 2:1 and affects individuals between the ages of 13 and 83, with a mean age of 55 years. In one of the large retrospective studies, which included 98 patients with CDC, most of the patients were whites (63%), followed by African Americans (27%).[4]

Although the clinical presentation is nonspecific, most of the patients present with gross hematuria, backache, weight loss, and mass per abdomen.[5] Patients with advanced or distant disease often present with constitutional symptoms like fever, weight loss, fatigue, or elevated acute phase reactants. Most studies showed equal involvement of the right and left kidneys.[6] Forty percent of the patients usually have metastasis at presentation, and the remaining 60% have localized disease. The most common sites for them to metastasize are the lymph nodes, lungs, and bone.[5] Tokuda et al reported 44% of lymph node metastasis and 32% distant metastasis.[7] Compared to clear cell RCC (8%), CDC (49%) has a

higher incidence of lymph node metastasis.[8] During relapse, they recur locally rather than distally. The mean time to recur locally after nephrectomy was 4.9 months and distally after 8.1 months.[9] As it is associated with early dissemination, they have high mortality rates. Less than one-third of the patients survived greater than 2 years. Median survival is 13 months, according to data from the National Cancer Database.

Blood investigations including complete blood count, liver and kidney function test, and viral markers are to be done during evaluation. Sonographic examination of the abdomen is done as an initial imaging in most cases to assess the echotexture of the solid components relative to renal parenchyma and renal sinus fat and evaluate the cystic component. Commonly, the solid component is hyperechoic to renal parenchyma and less echogenic than renal sinus fat. On CT, it is usually a solitary lesion involving the medulla that shows heterogenous enhancement. Fifty percent of them may have cystic components; renal contour is usually preserved; calcification with perinephric stranding and fat stranding may be seen. Lymphadenopathy is seen in around half of the patients and distant metastasis is seen in one-third of the patients. On magnetic resonance imaging (MRI), the tumor shows a mixed signal, which is isointense on T1 and a shorter signal on T2-weighted images with irregular or round borders, and it also shows mild to moderate uneven enhancement within the tumor in perfusion images.[10,11] In another study, 17% of the cases were associated with tumor thrombus in the venous system, and 44% had metastasis at presentation, which analyzed 74 cases of CDC over 20 years.[5] CT of the thorax is done to rule out lung metastasis as it is a common site for metastasis. Bone is a common site of metastasis, so a bone scan may be done. In clear RCC, FDG PET CT is not indicated for staging due to physiological excretion of FDG from kidneys, whereas CDCs are found to have marked avidity in FDG PET CT.[12]

Grossly, the lesion is infiltrative, which is firm gray or white; it involves the medulla but often involves both the cortex and the medulla. Hemorrhage, necrosis, and cystic changes may be observed. There may be renal vein invasion and satellite nodules. It often infiltrates perirenal and renal sinus fat. Microscopically, the medulla is involved by the tumor with mainly interstitial growth patterns, formation of tubules, desmoplastic stromal reaction, fiber hyperplasia, and detached single cells with a hobnail surface. They also have high-grade cytological features with infiltrative growth patterns. Solid, sheet-like, nested, cord-like papillary growth may also be seen. They have large and pleomorphic nuclei with prominent nucleoli and coarse chromatin. Numerous mitotic figures, apoptotic cells, and necrosis may be seen. Intracytoplasmic and intraluminal mucin are also seen often. Some of them also show sarcomatoid differentiation. There may be dysplastic changes in the tubular epithelium lining the collecting ducts. Regional lymph node involvement and lymphovascular invasion may be observed.[13] Immunohistochemistry shows CK19, CK7, 34BE12, and vimentin positivity. Previous studies also showed positivity for Epithelial membrane antigen (EMA), peanut lectin agglutinin, and Ulex europaeus agglutinin 1.[14] Other pathological differential diagnoses are papillary RCC, high-grade urothelial carcinoma, mucinous tubular and spindle cell carcinoma, medullary carcinoma, fumarate hydratase–deficient RCC, tubulocystic carcinoma, and metastatic carcinoma.[15]

Her2 neu amplifications have been reported in a few studies, ranging from 8 to 45%. Other common genomic alterations seen are in *NF2* (29%), *SETD2* (24%), *SMARCB1* (18%), *CDKN2A* (12%), *PIK3R2*, *BAP1*, *DNMT3A*, *VHL*, *HRAS*, and *FH*. Common chromosomal alterations are loss of 8p,16p, 9p, and 1p, and gain of 13q. Immunogenic alterations in the proteins are CD276, EBI3, PTPRC, NCK1, IL 18, CD3E, CD28, NCK2, ICOSLG, IL4, L2, and IL12B.[16] Six new recurrent somatic mutated genes, including RBM14, MTUS1, DST, GAK, RNF213, and XIRP2y, were identified in another study. CDKN2A-mediated p53/RB1 pathway is the most frequently altered pathway.[17]

In a localized CDC, treatment is radical nephrectomy followed by adjuvant chemotherapy. Radical nephrectomy includes removal of the kidney along with perinephric tissues, Gerota's fascia, and ipsilateral adrenal gland. There is no role for lymph node dissection.[18] A pathology report of the nephrectomy specimen includes the histology with tumor size, invasion of perirenal and renal sinus fat, and margins status. Adjuvant chemotherapy is with gemcitabine and cisplatin/carboplatin. There is no established role for adjuvant radiotherapy. For metastatic CDC, except for palliative reasons, radical nephrectomy alone is not helpful as it is very aggressive.[19] However, some studies state that the absence of renal surgery was associated with poor outcomes.[5] In a systematic review, the gemcitabine and cisplatin regimen showed a 26% objective response rate in CDC. Hence, this regimen is considered first line in metastatic CDC (►**Table 1**).[20,21] There is no established second-line therapy. In a study including 34 patients with CDC, immunotherapy with IL2, interferon-α, and interferon-γ showed no response.[7] Also, Motzer et al presented 15 patients with CDC treated with immunotherapy with no effect.[22] In a study, Her2 protein expression was assessed by immunohistochemistry and fluorescence in situ hybridization, and 8% of them were found to be Her2 positive.[23] Other studies showed 45% Her2 positivity, and given this, double Her2 blockade has been tried in disseminated CDC.[24,25] Also, there are case reports where sunitinib has been used with partial response. Nivolumab is associated with partial response and improvement in performance status.[26] There are case reports where palbociclib has been tried in patients with Cyclin dependent kinase inhibitor 2A (CDKN2A) homozygous deletion with partial response achieved.[27] Case series showed good disease control with sunitinib, sorafenib, and temsirolimus (►**Table 1**).[28] The caBozantinib in cOllecting ductS Renal Cell cArcinoma (BONSAI) trial included 25 patients to determine the efficacy of cabozantinib and showed an objective response rate of 35%.[29] Currently, one trial has recruited patients with CDC to look for the efficacy of cabozantinib with ipilimumab and nivolumab (NCT04413123). RadiCal study is a phase 2 study recruiting patients with CDC with bone metastasis where radium-223 dichloride is added to cabozantinib (NCT04071223). There are studies

Table 1 Recent articles on treatment of collecting duct carcinoma and results

Study	Cases	Treatment	Results
Qian et al[6]	12 cases 25% metastatic	• 91% underwent surgery	1-y overall survival is 45% 2-y overall survival is 36% 5-y overall survival is 8%
Chen et al[5]	74 cases 43% metastatic	• 82% underwent surgery • 10% received chemotherapy, out of which 4% had partial response and 2.7% had stable disease • 1.4% received chemotherapy + immunotherapy and had stable disease • 4.1% received targeted therapy and did not show any response • 1.4% received targeted therapy with immunotherapy and had partial response	Median overall survival is 24 mo Overall survival in metastatic disease is 11 mo
Oudard et al[20]	23 cases 100% metastatic	• 87% underwent surgery • All of them received chemotherapy with gemcitabine and cisplatin • 4% had complete response • 22% had partial response • 44% had stable disease • 30% had progressive disease.	Progression-free survival: 7 mo Overall survival: 10 mo
Procopio et al[28]	7 cases 100% metastatic	• 85% underwent surgery	4 patients received sorafenib: 33-mo disease control in 1 patient and early progression in other 3 patients 2 patients received temsirolimus: 6-mo disease control in 1 patient and early progression in the other 1 patient received sunitinib: early progression

planned to evaluate the efficacy of axitinib in metastatic CDC (NCT06211114). As CDC has a poor prognosis, an in-depth exploration of molecular characterization is essential to find a targetable process. Due to the rarity of the disease, multi-institutional prospective studies should be conducted to find the optimal treatment.

Conclusion

CDC of the kidney is an aggressive tumor with a poor prognosis and limited treatment options. Gemcitabine and platinum are the chemotherapy of choice in the adjuvant and metastatic setting. Further treatment options are limited. The roles of immunotherapy and targeted therapy are being studied. In such rare cases, molecular studies are essential to find out a targetable process.

Written Informed Consent Statement

Written informed consent was obtained from the patient for publication of this case report.

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Conflict of Interest

None declared

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