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Collecting duct renal cell carcinoma: a single centre series and review of the literature

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Introduction Collecting duct, or Bellini duct, renal cell carcinoma (CDRCC) is a rare tumour, comprising only 0.4–2% of all renal cell carcinoma. The goal of this study was to evaluate the cases in our institution and look at current available literature.

Material and methods We searched all data on renal cell tumours in our institution between 2011 and 2021 and identified four cases with confirmed CDRCC pathology. Important features were listed and analysed. We also reviewed current available literature and compared it to our case series.

Results All cases were men with a median age of 63.5 years. All were symptomatic at presentation. Two patients presented with flank pain and two with gross haematuria. Three patients had stage IV disease at time of presentation and one stage III disease. All cases had clear Bellini duct renal cell carcinoma appearance on microscopy with infiltrative tubular architecture and high-grade nuclear features. Immunohistochemic (IHC) staining was performed for diagnostic confirmation. Three patients underwent radical nephrectomy and received adjuvant chemotherapy. One case had kidney biopsy for diagnostic confirmation and received first line chemotherapy. Immunotherapy or tyrosine kinase inhibitor (TKI) were started for second, third or fourth line of treatment. Median overall survival after diagnosis was 11 months.

Conclusions CDRCC is a rare subtype of renal cell carcinoma with poor prognosis, typically presenting in a more advanced or metastatic stage. Diagnosis can be challenging. Multimodality treatment should be considered using radical surgery and systemic treatment.

Key Words: Bellini duct renal cell carcinoma ‹› collecting duct renal cell carcinoma ‹› multimodality treatment ‹› oncology ‹› urology

INTRODUCTION

Collecting duct renal cell carcinoma (CDRCC), or Bellini duct renal cell carcinoma, is a rare tumour, comprising 0.4–2% of all renal cell carcinoma [1]. CDRCC's clinical presentation is typically advanced and its course aggressive, associated with a poor prognosis [2]. Patients typically present with haematuria or flank pain from local extensive disease. Diagnosis can be challenging. Radiological features on computed tomography (CT) or nuclear magnetic resonance imaging (NMR) are often non-specific and can vary [3]. Histology differs from classic RCC subtypes and can show some similarity to other aggressive medullary tumours (e.g. renal medullary carcinoma) or upper tract urothelial cell carcinoma (UTUC) because of the epithelial origin of CDRCC [4, 5]. The latter explains the use of chemotherapeutic regimens, after surgical resection if feasible, rather than tyrosine kinase inhibitor (TKI) or immunotherapy (IO) as a systemic treatment in most series [6]. The available literature consists predominantly of case reports, and three larger series worldwide [7, 8, 9]. The goal of this

study was to evaluate the cases in our institution and summarize current literature.

MATERIAL AND METHODS

We searched all data on renal cell tumours in our institution between 2011 and 2021. All CDRCC diagnoses were identified and medical records were retrospectively analysed. The most important characteristics were reviewed and listed in Table 1. We used descriptive statistical analysis in Microsoft Office Excel 2011®.

We performed a research of the literature using Medline and Pubmed. The databases were searched using terms 'Bellini Duct', 'Collecting Duct' and 'Renal Cell Carcinoma'. We narrowed our search with full text availability. All papers found, were checked manually for eligibility.

RESULTS

We found four cases with pathologically proven collecting duct histology in our centre. One case was not included in our review because of uncertain pathological differentiation with UTUC. The incidence of CDRCC in all renal cell tumours at our institution was 0.7%. Table 1 shows all features. All cases were men with a median age of 63.5. Two patients presented with flank pain and two with gross haematuria. The majority got a CT scan of the abdomen for diagnostic work-up. Imaging was not specific for CDRCC, although an infiltrative, medulla-originated growth of the tumour and loss of renal architecture were recurrent features (see Figure 1). One case also showed a more cystic presentation. Mean tumour size was 9 cm (range 7.5–11.5 cm). Three patients had stage IV disease at time of presentation and one stage III disease. All had a locally advanced and/or metastatic presentation. Pathology reports showed high-grade tumour histology. All cases had clear Bellini duct renal cell carcinoma appearance on microscopy with infiltrative tubular architecture and high-grade nuclear features. We found immunohistochemic (IHC) staining for diagnostic confirmation in all cases. IHC was helpful in differentiating CDRCC from other renal tumours or UTUC. In two cases for example GATA3 negativity helped in the exclusion of UTUC. Also, the combination of positive staining for Pax8 and negative staining for CD10/CAIX

Table 1. *Features of patients with collecting duct renal cell carcinoma*

Case	Gender	Age (years)	Reason for consultation	Radiologic features	Tumour size	TNM	Treatment	Pathology	Survival (months)
1	Male	68	Incidental finding	CT-scan: cystic neoplasia, with hyperdensity, calcifications and irregular border	9 cm	T3aN1M1 Stage IV	Surgery Radical nephrectomy + LND Systemic treatment 1. Adjuvant CTX: carbo+ gem 2. Pembrolizumab (IO)	High-grade tumour, clear Bellini duct IHC: Pax8+, CD10-, Gata3+, CAIX-	10
2	Male	59	Flank pain and gross haematuria	CT-scan: expansive and infiltrative lesion with calcifications	7.5 cm	T4N1M1 Stage IV	Surgery / Systemic treatment 1. Immediate CTX: cis+gem 2. Nivolumab (IO) 3. Pazopanib (TKI) 4. Cabozantinib (TKI)	High-grade tumour, clear Bellini duct with infiltrative tubular architecture and atypical nuclei IHC: Pax8+, CD10+/-, CKH-	27
3	Male	53	Flank pain	CT-scan: loss of renal architecture, infiltrative aspect, near collecting system	8 cm	T3aN1M0 Stage III	Surgery Radical nephrectomy + LND Systemic treatment 1. Adjuvant CTX: carbo+gem 2. Nivolumab (IO)	High-grade tumour, clear Bellini duct carcinoma IHC: Pax8+, AMACR-, Gata3-	12
4	Male	81	Gross haematuria	CT-scan: loss of renal architecture, infiltrative aspect	11.5 cm	T4N1M0 Stage IV	Surgery Radical nephrectomy Systemic treatment Adjuvant CTX: carbo+gem	High-grade tumour; clear Bellini duct carcinoma with infiltrative tubular architecture and atypical nuclei IHC: CD10-, CKH+, GATA3-	10

NMR – nuclear magnetic resonance scan; LND – lymph node dissection; CT – computed tomography; CTX – chemotherapy; Cis – cisplatinum; Carbo – carboplatinum; Gem – gemcitabine; IO – immuno-oncology; IHC – immunohistochemistry; UTUC – upper tract urothelial cell carcinoma; TKI – tyrosine kinase inhibitor

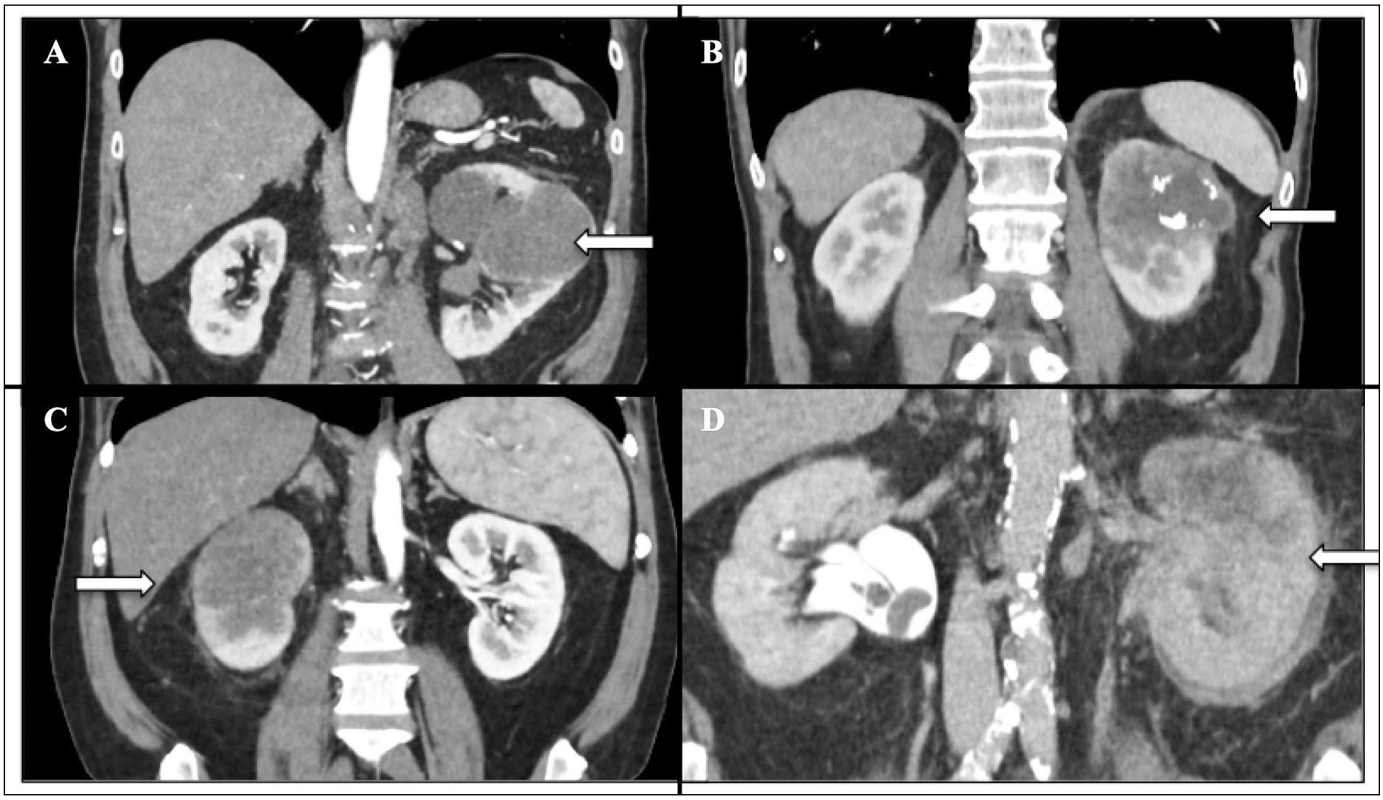

Figure 1. *Computed tomography scan showing collecting duct, or Bellini duct, renal cell carcinoma in all cases. The tumour is marked with a white arrow. (A: case 1; B: case 2; C: case 3; D: case 4).*

was helpful in our first case. The specific pathologic features are depicted in Table 1. Radical nephrectomy was performed in three cases. In the other, kidney biopsy confirmed histologic diagnosis. All patients received systemic (adjuvant) treatment with chemotherapy in first line (platinum and gemcitabine combination). Only when progression occurred and the patient was still fit enough IO or TKI were started for second, third or fourth line of treatment. This happened in three cases following multidisciplinary oncologic meeting and following former data. Median overall survival after diagnosis was 11 months.

DISCUSSION

Collecting duct renal cell carcinoma is a rare and aggressive disease, accounting for 0.7% of all renal cell cancers at our institution. As in our case series, diagnosis is often made in an advanced or metastatic stage. This explains the poor prognosis and limited response to disease management. When detected at an early stage, cure can be obtained by means of radical surgery, but this only applies to a small number of cases [1, 4]. Overall median survival is estimated at 13 to 58.8 months in the literature. Sui et al. reported an overall survival of 13.2 months after large-scale database analysis [1, 7]. We report an overall survival of 11 months, which is similar.

Most patients are male, being in the 4th to 6th decade of life and presenting with gross haematuria and/or flank pain, as seen in our case series. [5, 10]. These complaints resemble the often advanced stage of presentation.

Radiological diagnosis can be difficult. Yoon et al. emphasize that imaging has limited specific features for CDRCC differentiation: medullary location, weak and heterogeneous enhancement, involvement of the renal sinus, infiltrative growth, preserved renal cortex and possible cystic component [3]. In our cases the infiltrative growth and loss of normal renal architecture stand out. When looking at histology, the literature demonstrates various pathologic features with only few recurrent characteristics: infiltrative and irregular tubular and tubulopapillary structures, myxoid to fibrosclerotic desmoplasia, presence of mucin and variable amount of necrosis. Also, IHC staining can help the CDRCC diagnosis, especially in the exclusion of other renal cancers (e.g. ccRCC, papillary RCC, chromophobe RCC or renal medullary carcinoma) or UTUC. CDRCC often

express high molecular weight keratins (e.g. CK19, CK7) and Pax2/8. Positive staining for Ulex europaeus lectins is also often described but not used in our cases. Literature proposes the use of p63 and GATA3 staining for differentiation with urethelial cell carcinoma (UCC). The latter was also used in two of our patients [10–13].

In our case series three patients underwent radical nephrectomy. All did so in a cytoreductive manner, because of advanced disease at presentation. There is no literature clarifying the place of cytoreductive nephrectomy in treatment of advanced CDRCC. Because of limited response to current systemic treatment, at present cytoreductive nephrectomy in conjunction to systematic treatment is suggested when feasible or for local symptom control [14]. In case of early detection and only localised CDRCC, radical surgery is the first choice of treatment [15].

All patients in our series had systemic treatment by means of combination chemotherapy: gemcitabine with platinum-based chemotherapy. Only in further lines of therapy, immunotherapy or TKI was introduced. It is difficult to study the optimal treatment in a prospective trial, because of the rarity of the disease. Due to its epithelial origin at the collecting ducts of Bellini, most studies suggest treatment overlap with UTUC rather than ccRCC. When looking at chemotherapy only small prospective phase II trials are available. Oudard et al. investigated platinum and gemcitabine combination chemotherapy in 23 previously untreated CDRCC patients. Objective response rate (ORR) was 26%. Progression-free survival (PFS) and overall survival (OS) were 7.1 and 10.5 months respectively [16]. Also, a more recent Chinese prospective phase II trial investigated combination therapy (gemcitabine and cisplatin and sorafinib) in 26 patients. PFS was 8.8 months, OS was 12.5 months, ORR was 30.8% [17]. The latest prospective phase II trial is still ongoing and investigates triple therapy with gemcitabine, platinum-based chemotherapy and bevacizumab. The trial was initiated after an interesting response in five patients as first line treatment: three cases with partial response, one case with stable disease and one case with complete remission [18]. Regarding targeted therapy, no prospective data exist. Tyrosine kinase inhibitors are excessively investigated for ccRCC but only small studies focused on non-ccRCC and CDRCC. There are some small case series showing partial response for sunitinib and sorafenib [19, 20, 21]. Immunotherapy trials on CDRCC are also not (yet) available. When looking at the literature there are 3 case reports suggesting nivolumab treatment, especially in PD-L1 positive patients, but large prospective trials are needed for further conclusions [22, 23, 24].

CONCLUSIONS

CDRCC is a rare subtype of renal cell carcinoma, typically presenting in a more advanced or metastatic stage. Diagnosis can be challenging. Multimodality treatment should be considered using radical surgery and chemotherapy. The role for targeted therapy in CDRCC is still undetermined. Survival is poor. Only in early detection and localised disease, complete cure can be obtained by radical surgery.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

All data that support the findings of this article are available on request from the corresponding author.

Informed consent of all patients was obtained for this study.

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