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# Synchronous Collecting Duct Carcinoma and Papillary Renal Cell Carcinoma: A Case Report and Review of the Literature

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**Abstract.** *The coexistence of multiple and synchronous primary neoplasms in the same organ (including kidney) has only rarely been described in the literature. We herein present a case of collecting duct carcinoma (CDC) combined with papillary renal carcinoma (RCC) having a 57-month disease-free survival. CDC is a rather rare and aggressive neoplasm of the kidney. Sharing probably the same embryological origin, synchronous or metachronous association with in situ or papillary transitional cell carcinoma (TCC) may be found; association with RCC has been only once reported in the literature. The high incidence of c-erbB-2 oncogene amplification in CDC further characterizes this tumor as a separate entity from renal cell carcinoma, and shows some genetic characteristics in common with TCC. The histological diagnosis of Bellini CDC can be confirmed by the positive immuno-histochemical staining with a collecting duct marker and distal tubule marker and negative staining with a proximal tubule marker.*

Bellini's collecting duct carcinoma (CDC) is an unusual renal neoplasm with a poor prognosis. Its origin is not entirely known, although it is thought to arise from the distal collecting duct system, whereas clear cell renal carcinoma (RCC) may originate from the proximal tubular epithelium (1).

The coexistence of multiple and synchronous primary neoplasms in the same organ (including kidney) has only rarely been described in the literature. Some cases of rare synchronous occurrence of transitional cell carcinoma (TCC) and RCC have been reported. CDC was found to be associated with TCC (2) and with RCC (3).

Recently, we had the opportunity to examine one such case of synchronous CDC combined with RCC: the clinical, radiological and histopathological findings are reported. The clinical outcome was extremely favorable.

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## Case Report

A 70-year-old man presented, for some months, lasting inconstant hematuria and left flank pain. Ten years previously, he had undergone an endoscopic procedure for superficial TCC of the bladder. US and CT scan (Figure 1) showed a left 5-cm-large renal mass developing towards and infiltrating the upper major calyx with evidence of tumor extension into the adjacent renal vein and artery. At arteriography (Figure 2) the mass resulted avascular, while retrograde pyelography (Figure 3) suggested it could be a TCC involving the upper collecting system. Urinary cytology showed papillary-like cell-aggregates. Radical nephrectomy was performed, without ureterectomy, as frozen sections showed that it was not TCC. Histopathological examination demonstrated two tumors: one, centered on the renal medulla, grossly infiltrating the upper major calyx (collecting duct carcinoma), and another involving the upper renal pole and extending to the capsule (papillary renal cell carcinoma). After 57 months, the patient is still free of relapse.

## Materials and Methods

The left nephrectomy specimen was examined grossly and representative tissue blocks were taken from the tumors and the adjacent renal parenchyma. They were fixed in 10% buffered formalin and embedded in paraffin. Four-micrometer sections were cut and stained with hematoxylin and eosin. Immunohistochemical studies using a panel of antibodies (UEA-1, CK 7, CK 19 and c-erb B2) were carried out (Table I).

## Results

*Gross findings.* There was a solid tumor sited within the renal medulla measuring 5.3 cm in maximum diameter. It had a homogeneous whitish cut surface and firm consistency. It

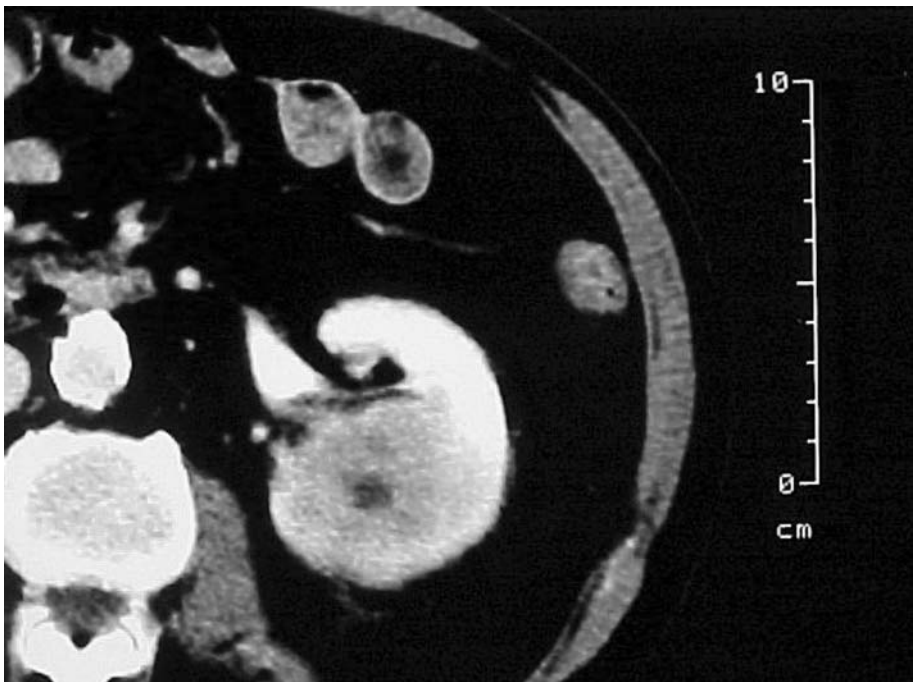


Figure 1. *CT-scan: a 5-cm-large renal mass protruding into the central sinus having minimal contrast enhancement.*

Table I. *Immunohistochemical panel of antibodies used for our case.*

| | |
|---|---|
| Ulex Europeus Agglutinin-1 | UEA-1 |
| Low molecular weight cytokeratin | CK 7 |
| Low molecular weight cytokeratin | CK 19 |
| Antibody for oncogene | c-erb B2 |

infiltrated the upper major calyx and infundibulum. The tumor corresponded well to the large solid mass detected on US and CT scan. Another nodule, involving the upper renal pole, bulging outward and invading the kidney capsule, was found. It was 5 mm in maximum dimension with a white cut surface. The adjacent renal parenchyma was normal, while surgical margins, adrenal gland and exported loco-regional lymph nodes were free of tumor involvement.

*Microscopic findings.* Histologically, the medullar tumor consisted of medium, uniform cells arranged in tubular pattern (Figure 4) with desmoplastic stroma and a brisk inflammatory reaction (Figure 5). The tumor cells had round to oval nuclei with small inconspicuous nucleoli, and fairly abundant and eosinophilic cytoplasm. Extensive destruction of renal medullar tissue was found with infiltration of the renal cortex glomeruli and dysplasia of the collecting duct epithelium.

As previously described, another nodule involving the renal cortex and invading the capsule was found. This cortical nodule had a papillary growth pattern (Figure 6a) with numerous psammoma bodies. The cells were uniform with inconspicuous cytoplasm, ovoid nuclei and rare nucleoli.

*Immunohistochemical studies.* The tumor cells of the medullar neoplasm reacted with antibodies to cytokeratin pool CK19 and UEA-1 (Figure 7b,c). This is the staining pattern of normal distal tubular epithelium. CK7 resulted negative (Figure 7a). A focal, faint perceptible membrane staining was found in less than 10% of the tumor cells, with antibodies for c-erb B2 (Figure 7d).

The tumor cell of the cortical neoplasm was strongly positive for CK7 (Figure 6b).

## Discussion

The coexistence of multiple synchronous primary neoplasms in the same kidney has been rarely described in the literature. The most frequent combination is RCC and TCC. Hart *et al.* reviewed 22 cases reported in the English literature (4). CDC was found to be associated with TCC (2 cases) (2) and with RCC (1 case) (3).

Bellini CDC represents a subgroup within renal carcinoma with an incidence of 0.4-2% (2) of all renal tumors. It is a rare neoplasm with less than 150 cases described in the literature to date (5, 6), of which 41 were in

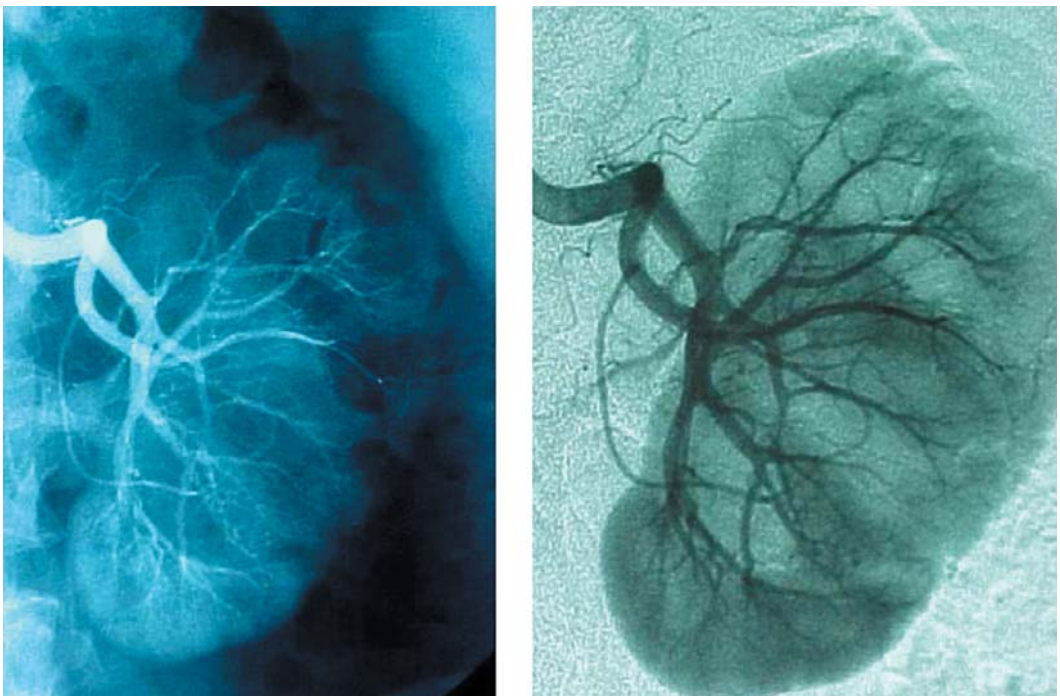

Figure 2. *Arteriography showing a completely avascular mass.*

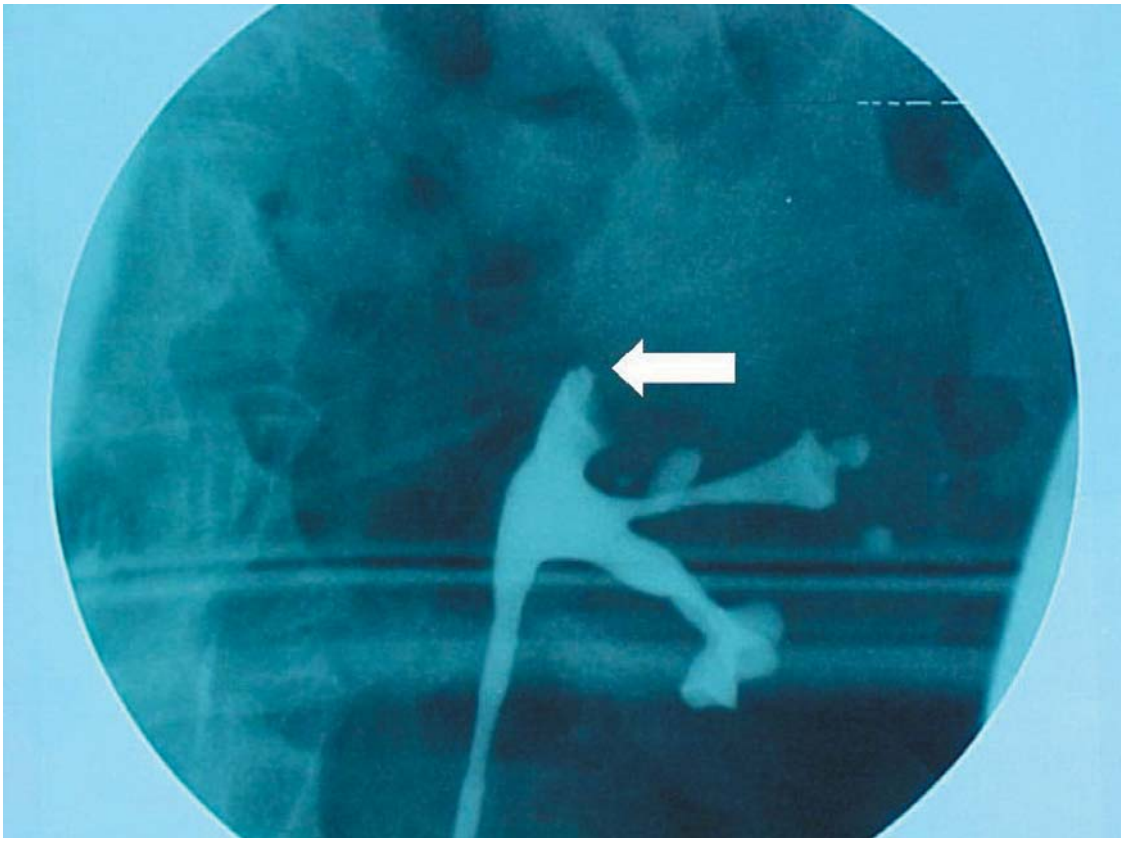

Figure 3. *Retrograde (high pressure) pyelography showing an endoluminal minus (arrow) causing obstruction of the upper collecting system.*

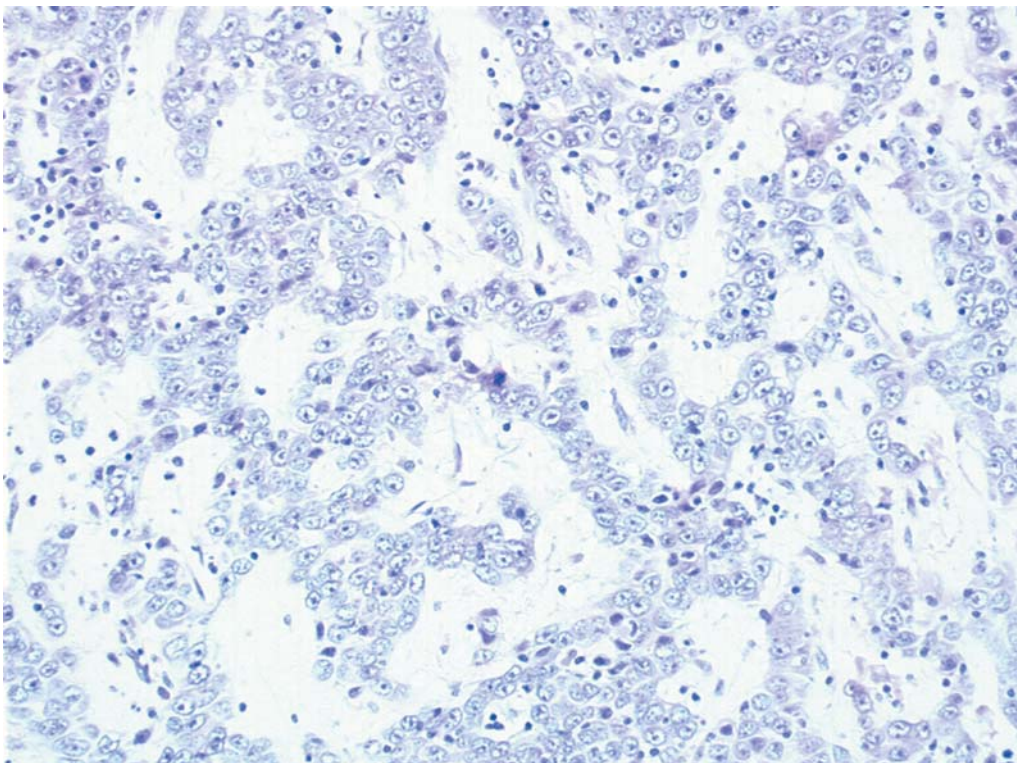

Figure 4. *CDC with tubular growth pattern.*

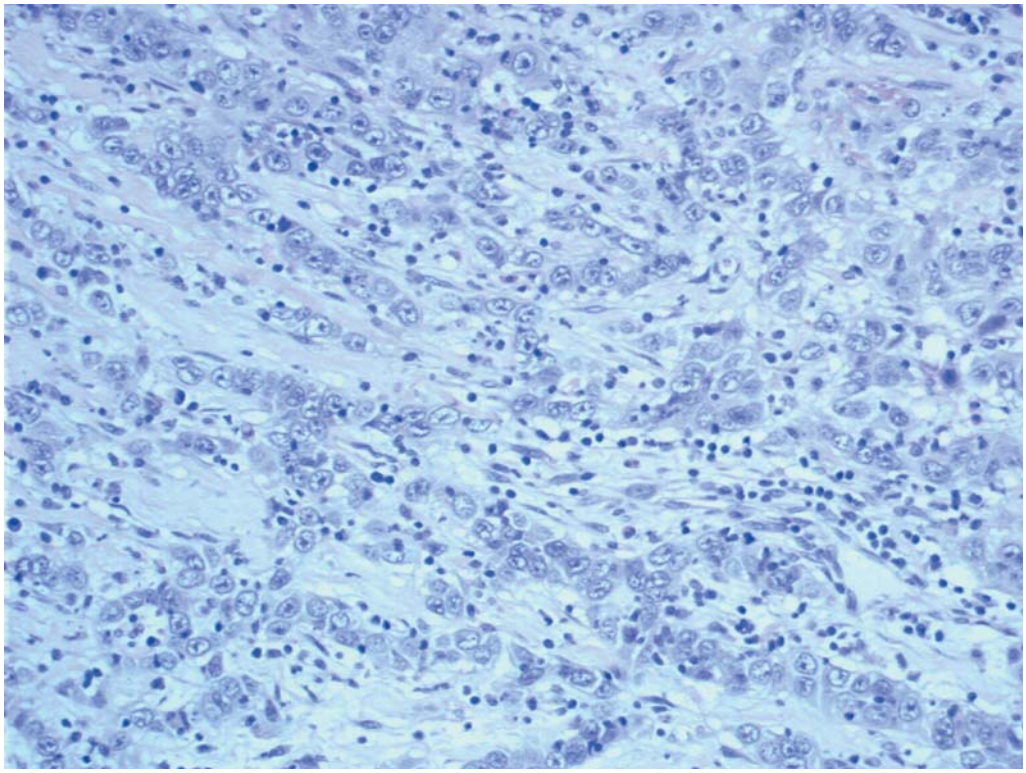

Figure 5. *CDC with desmoplastic stroma and inflammatory cells.*

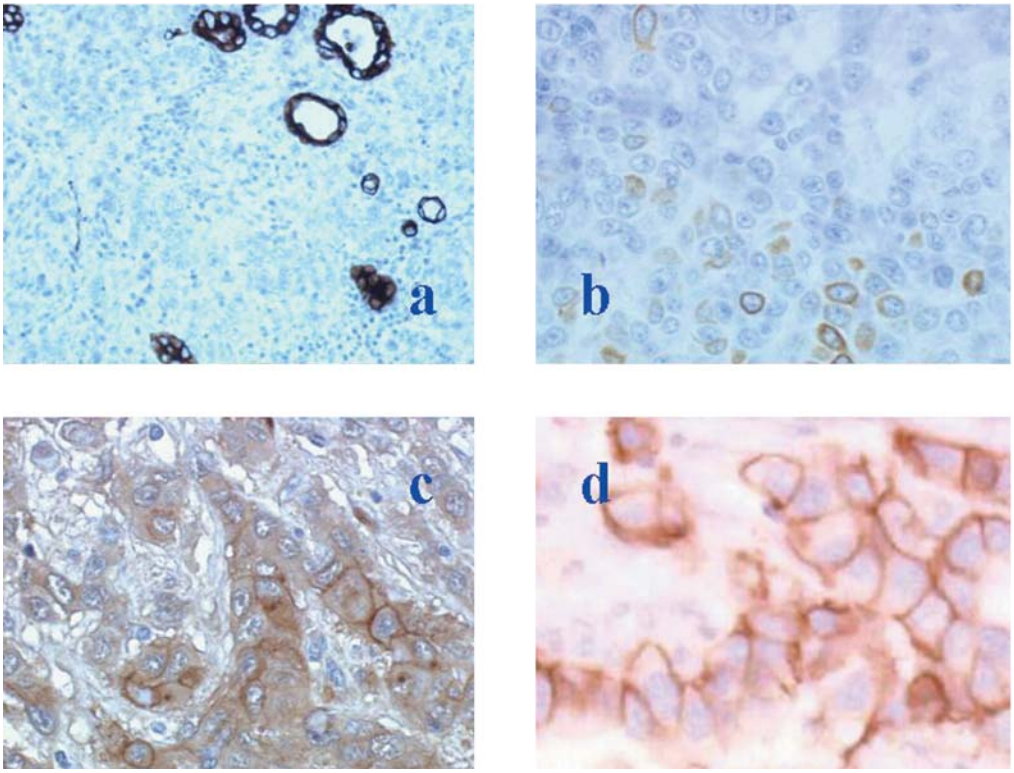


Figure 6. *CDC with most of the tumor cells displaying positive immunoperoxidase stain by CK 7 (a), CK19 (b), UEA-1 (c) and c-erb B2 antibodies (d) (original magnification, x 400).*

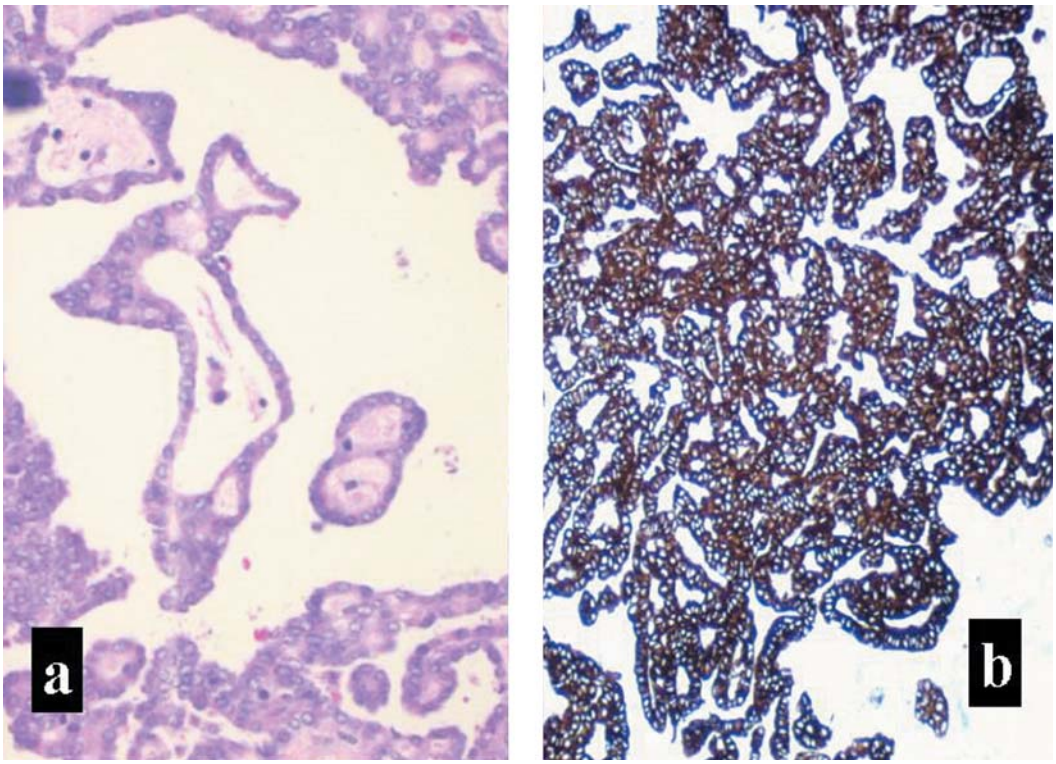


Figure 7. *Papillary RCC with papillary growth pattern (a) and positive immunoperoxidase stain by CK7 antibodies (b) (original magnification, x200).*

Table II. *Long-term disease-free survival CDC patients in the reported series (review of the literature).*

| | Staging (TNM 1997) and Fuhrman grade | Survival |
|---|---|---|
| Chao *et al.*[5] | $T_1$ $G_2$ $N_0$ | 5 yrs |
| Peyromaure *et al.*[31] | $T_1$ $G_x$ $N_0$ | 13 mos |
| | $T_3$ $G_x$ $N_0$ | 17 mos |
| Méjean *et al.*[37] | $T_{3b}$ $G_3$ $N_0$ | 100 mos |
| | $T_1$ $G_4$ $N_0$ | 99 mos |
| Dobronski *et al.*[38] | $T_3$ $G_x$ $N_0$ | 12 mos |
| Matsumoto *et al.*[12] | $T_{1a}$ $G_x$ $N_0$ | 24 mos |
| de la Pena Zarzuelo *et al.*[39] | $T_1$ $G_2$ $N_0$ | 41 mos |
| | $T_1$ $G_2$ $N_0$ | 56 mos |
| | $T_{3a}$ $G_3$ $N_0$ | 32 mos |
| | $T_{3a}$ $G_3$ $N_0$ | 24 mos |
| Our patient | $T_{1(m)}$ $G_3$ $N_0$ | 57 mos |

Japan (7-21). A review of the available Anglo-Saxon literature reported about 64 cases (5). It occurs in a wide age range and predominantly in males (6).

CDC is a highly aggressive renal tumor (22), with a poor prognosis (mean survival 11.5 months (5)). Its histogenesis is still a matter of debate although a putative origin from collecting ducts has been proposed (14, 23-25). The collecting ducts share their embryological origin in Wolf's duct with the calyces, renal pelvis and ureter (6). This common embryological origin could justify its synchronous or metachronous association with *in situ* or papillary TCC in the adjacent renal pelvis (2), but not with papillary RCC. In fact, while CDC originates in the medullar collecting duct, a mesonephric structure, RCC originates from tissues having metanephric precursors.

CDC seems to belong to a broad spectrum of distal collecting duct carcinomas with different morphological traits: low-grade CDC (McLennan *et al.* (26) described this mucin-producing subtype of CDC) → CDC → renal medullary carcinoma (6) showing worsening prognoses. Genetic studies show that CDC is not clearly related to clear renal cell carcinoma but may be of heterogeneous origin: loss of heterozygosity of von Hippel Lindau gene (3p), of p16 (9p) and of p53 (17p) (25); loss of DNA sequences involving chromosomes 1, 2, 9, 11 and 18 and gain of DNA sequences affecting chromosome 16 and 20 were reported (27). Eighteen collecting duct carcinomas were studied by Polascik *et al.* (1) using highly informative microsatellite markers on all autosomal arms. This work suggests that the molecular events that contribute to the development of distal nephron tumors are distinct from those associated with the ethiology of proximal tubule renal cancer. The high incidence of c-erb B2 oncogene amplification in CDC further characterizes this tumor as a separate entity from renal cell carcinoma, and shows some genetic characteristics in common with TCC (28).

Reviewing the literature, we found only one other reference reporting the coexistence of CDC with RCC (3). Ours seems to be the first case with coexisting papillary RCC and CDC. Moreover, the patient also had a story of a previous low-grade bladder TCC.

The usual histopatological pattern of CDC is that of a tubular or tubulopapillary carcinoma with a desmoplastic stroma that often contains neutrophils (6, 29). Besides marked desmoplastic reaction, atypical hyperplastic changes can be found in the adjacent collecting ducts (30). Although light microscopy permits diagnosis of CDC on the basis of its histomorphological features, CDC can be confused histologically with other usual papillary RCCs (31). Thus, immunohistochemical identification of specific antigens is needed for differential diagnosis (6, 29-32). Positive immunohistochemical staining with a collecting duct marker (UEA-1) and distal tubule marker (EMA) and negative staining with a proximal tubule marker (Leu M1) are highly indicative of CDC (14, 17, 30, 31, 33).

Urinary cytology in CDC is another debated item: Nguyen and Schumann (15) reported that urine sediments of two reported cases with confirmed CDC showed malignant glandular cells in sheets with defined, variable, granular cytoplasm and oval, hyperchromatic nuclei containing micro- or macronucleoli. Fallick *et al.* (34) described a case of CDC associated with abnormal urine cytology yet not typical of TCC, suggesting a close relationship between the cytology and histology of this uncommon malignancy. Finally, Zaman *et al.* (35) reported that cytological specimens in two out of three patients who underwent resection for CDC were interpreted as TCC and one as reactive change.

CDC spreads aggressively and many patients have metastases at the time of presentation (6). Bone and lung metastasis and also extensive regional node involvement were reported (31). A fatal CDC, presenting with pleural metastases, arising from the right kidney in an 8-year-old child, was reported by Craver (34), while direct invasion of the liver was reported by Sue *et al.* (17), thus requiring radical nephrectomy and segmental hepatectomy. One case of tumor extension into the inferior vena cava was also described (16).

Although, according to some authors (2, 11), CDC should be suspected in cases when CT shows kidney maintaining the normal outer contours, with mass protruding into the central sinus and showing minimal contrast enhancement, often diagnosis is possible only after surgery. There are very few reports describing the tumor appearance at arteriography (10, 14). Some authors (7, 19) reported $^{67}$Gallium citrate uptake showing a potential utility of $^{67}$Ga scintigraphy in detecting Bellini CDC.

In non metastatic patients, nephrectomy seems to be the therapy of choice as the tumor usually displays highly aggressive behavior (10, 23, 36). Nevertheless, if imagistic procedures ($^{67}$Gallium imaging included) are suggestive of CDC, biopsy should be performed, as nephrectomy seems less useful in metastatic CDC (37). Some authors have proposed and performed adjuvant chemotherapy, usually employing TCC-indicated-for regimens: M-VAC (10, 18), doxorubicin + gemcitabine alternated with ifosfamide paclitaxel and cisplatin (CDDP) (22) and, recently, CDDP-gemcitabine regimen (32). Some complete response was reported (32), but relapse after chemotherapy is far from being uncommon. Interferon-α or IL-2 immunotherapy seems to have little effect in the adjuvant setting (32, 37) even if episodical responses were reported (31, 36). The role of adjuvant chemotherapy (21, 30) needs further evaluation and prognosis still remains poor.

This aggressive tumor has dismal prognosis and early diagnosis appears to be the only factor that may positively influence the survival. In the most conspicuous series, reported overall survival varied from 6-8 months (37), 11.5 months (5), to 20 months (39).

Long-term disease-free survival was however reported, particularly recently (Table II) in patients with non metastatic disease. In fact, ours is one of the few cases (*i.e.* 5) reported in the literature having a survival of more than 4 years, still without any sign of relapse.

## Conclusion

Collecting duct carcinoma is a rare renal cancer subtype; its association with other renal tumors is found exceptionally. In most of the cases, it has aggressive course and poor prognosis. In recent literature reviews, some cases with good outcome were, however, described. Current standard chemotherapy or immunotherapy treatment regimens have been found to be ineffective. Moreover, in case of metastatic CDC, even nephrectomy seems not to be useful except for palliative reasons.

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