Low-grade Collecting Duct Carcinoma Of The Kidney: A Potential Mimic Of Conventional Clear Cell Carcinoma

D Charney, J Tomasula

Citation

Abstract
Collecting duct carcinoma of the kidney is a well-known, but relatively uncommon tumor characterized by a high cytologic grade, desmoplastic stroma and a poor clinical outcome. Since 1979, however, there have been several reports of low-grade renal carcinoma of putative collecting duct origin. These low-grade tumors were extensively papillary, tubulopapillary or tubulocystic, with a low nuclear grade (usually Furhman grade 1 or 2). Most have conferred a benign follow-up course, even when treated only by partial nephrectomy. The previous reports of such tumors have been variably characterized immunohistochemically and ultrastructurally. We report the cases of a low-grade renal carcinoma of collecting duct origin, arising in the right renal lower pole of a 47-year-old-male with a history of gout and nephrolithiasis. Microscopically, the tumor showed a tubular and tubulocystic pattern and was composed almost exclusively of clear cells, closely mimicking conventional (clear cell) renal cell carcinoma. Tumor cells stained positively for PAS, showed droplet-like staining with Hale's colloidal iron, were variably alcian blue positive and were mucicarmine negative. They were reactive with immunohistochemical antibodies to peanut agglutinin (PNA), Ulex europaeus-1 agglutinin (UEA-1), pan-cytokeratin, CAM 5.2, cytokeratin 7, epithelial membrane antigen (EMA) and vimentin. Electron microscopy showed microvillous-lined tubules, desmosomes, and tonofilaments, with a paucity of mitochondria. The patient was treated by partial nephrectomy and has been without evidence of disease for a follow-up period of 10 months.

INTRODUCTION
Collecting duct carcinomas of the kidney are relatively uncommon neoplasms, generally regarded as high grade tumors expressing phenotypic markers of the normal renal collecting duct, which include high molecular weight cytokeratin (HMWK, 34+E12), Ulex europaeus-1 agglutinin (UEA-1), peanut agglutinin (PNA) and epithelial membrane antigen (EMA) [12,13]. These tumors are grossly situated in the renal medulla with a firm consistency and gray-white color. Microscopically, they are usually tubular or tubulopapillary with a high nuclear grade and markedly desmoplastic stroma. Clinical outcome is poor, with approximately 66% of patients dying of disease within 2 years of diagnosis [4].

In 1979, Cromie et al described a low-grade renal carcinoma characterized by a tubular and papillary microscopic pattern, low nuclear grade, absence of desmoplasia and apparent origin from collecting duct epithelium. Follow up clinical course was benign following radical nephrectomy [5]. Since that time, additional reports of low-grade renal carcinomas, apparently of collecting duct or distal nephron origin, have been reported, almost all having a benign follow-up clinical course following either radical or partial nephrectomy [6-10]. Most of these have been studied histochemically and immunohistochemically, with only 10 examined ultrastructurally [5,7,8]. The importance of the presently described case lies in its striking histologic similarity to conventional (clear cell) renal cell carcinoma, with which it might have easily been confused.

CASE REPORT
A 47-year-old white male was found to have a 2.0-cm solid mass at the lower pole of his right kidney during evaluation for microscopic hematuria. His past medical history was significant for Crohn's disease, type II Diabetes Mellitus and gout. He suffered a single episode of nephrolithiasis four years prior, with intermittent left flank pain and hematuria. Chemical analysis showed the stones to be composed of uric acid. His medications included mesalamine, glyburide and rofecoxib. His physical examination was unremarkable. Laboratory values were significant for serum uric acid level of 7.0 mg/dl. Urinalysis revealed 0-3 white blood cells/hpf, 30-40 red blood cells/hpf, 3-5 epithelial cells/hpf and trace proteins. Renal ultrasound showed a right kidney of 12.4 cm and a left kidney of 12.2 cm with calculi identified within...
the collecting system. A CT scan of the abdomen showed multiple calculi within the pelvis of the left kidney and a 2.0 cm mass in the lower pole of the right kidney (figure 1).

Figure 1
Figure 1. An approximately 2.0 cm round to ovoid mass is seen within the right kidney on CT scan, spanning both cortex and medulla (arrow).

The mass in question did not enhance with intravenous contrast. Magnetic resonance imaging also revealed a 2.0-cm ovoid area of mildly increased T2 signal intensity and intermediate T1 weighted sequences in the inferior pole of the right kidney. The lesion did then enhance after contrast administration. Nephron sparing surgery (partial nephrectomy) was performed and the specimen was sent for pathologic evaluation.

**PATHOLOGIC FINDINGS**

The specimen was fixed in 10% neutral buffered formalin and routinely processed. The gross specimen consisted of a 3.3 x 3.0 x 2.2 cm. wedge-shaped portion of renal parenchyma with a portion of capsule and a rim of intact cortex overlying a 1.8 cm round to ovoid pink-red circumscribed tumor mass situated within the renal medulla.

Microscopically, the tumor was composed of tubular and acinar structures, as well as some cystically dilated tubules, lined by cuboidal cells with mostly clear cytoplasm (Figure 2).

**Figure 2**

Figure 2. The tumor is composed of tubular structures lined by clear to granular cells containing only mildly pleomorphic nuclei (H&E, 200X).

Some dilated spaces were filled with red blood cells and their lining cells contained cytoplasmic hemosiderin granules. There was focally abundant intercellular mucoid material, which stained positively for alcian blue, but not mucicarmine. The tumor cells showed droplet-like staining with Hale's colloidal iron, and similar droplet-like staining with PAS stain. The tumor itself was well demarcated from the renal parenchyma and, around much of its perimeter, showed bundles of hypertrophic smooth muscle. Dysplastic changes of distal tubules or collecting ducts were not seen. Immunohistochemical results are delineated in tables 1 and 2.
Table 1. Immunohistochemical analysis of renal tumor

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Source</th>
<th>Case</th>
<th>Dilution</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCC</td>
<td>Huntsman, Huntsville, 3, USA</td>
<td>668422</td>
<td>1:100</td>
<td>negative</td>
</tr>
<tr>
<td>CD21</td>
<td>Huntsman, Huntsville, 3, USA</td>
<td>56326</td>
<td>1:100</td>
<td>positive</td>
</tr>
<tr>
<td>CK19</td>
<td>Huntsman, Huntsville, 3, USA</td>
<td></td>
<td>1.5</td>
<td>negative</td>
</tr>
<tr>
<td>Epithelial membrane antigen (EMA)</td>
<td>Dallas, Carpentaria, CA</td>
<td>E29</td>
<td>1:40</td>
<td>positive, monomorphism and paranuclear dot</td>
</tr>
<tr>
<td>Pancreatin</td>
<td>Elmhurst, Des Moines, 2, IA</td>
<td>45.51</td>
<td>1:40</td>
<td>positive, strongly staining in collecting duct cell and epithelial tumor (with ducts of torus)</td>
</tr>
<tr>
<td>(3, 2, and 5)</td>
<td>Houston, TX, 3, USA</td>
<td>BM2-2</td>
<td>1:95</td>
<td>positive</td>
</tr>
<tr>
<td>(3, 2, and 5)</td>
<td>Dallas, Carpentaria, CA</td>
<td></td>
<td>1:40</td>
<td>negative</td>
</tr>
<tr>
<td>CK7</td>
<td>Dallas, Carpentaria, CA</td>
<td>07771220</td>
<td>1:10</td>
<td>positive</td>
</tr>
<tr>
<td>CK19</td>
<td>Dallas, Carpentaria, CA</td>
<td>E9038</td>
<td>1:20</td>
<td>negative</td>
</tr>
<tr>
<td>EMA</td>
<td>Dallas, Carpentaria, CA</td>
<td>541122</td>
<td>1:50</td>
<td>negative, keratin, non-epithelial cells did not stain</td>
</tr>
<tr>
<td>Pancytokeratin</td>
<td>Veterans, Badalona, CA</td>
<td>Lectin</td>
<td>1:500</td>
<td>positive</td>
</tr>
<tr>
<td>Urothelial antigen</td>
<td>Veterans, Badalona, CA</td>
<td>Lectin</td>
<td>1:20</td>
<td>positive</td>
</tr>
<tr>
<td>Vimentin</td>
<td>Dallas, Carpentaria, CA</td>
<td>59</td>
<td>1:10</td>
<td>positive</td>
</tr>
</tbody>
</table>

Table 2. Reported cases of low grade renal carcinoma of putative collecting duct origin

<table>
<thead>
<tr>
<th>Author, Reference number</th>
<th>Number of patients</th>
<th>Microscopic pattern</th>
<th>Tumor nuclear grade</th>
<th>Dysplastic change of collecting ducts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Czernie et al, 5</td>
<td>1</td>
<td>Clear cell, tubular and papillary</td>
<td>Low</td>
<td>Not specified</td>
</tr>
<tr>
<td>O’Brien et al, 8</td>
<td>1</td>
<td>Papillary</td>
<td>Low</td>
<td>Not specified</td>
</tr>
<tr>
<td>Hermigier and Rockwitz, 6</td>
<td>2</td>
<td>Papillary, contained within nephron adenocarcinoma</td>
<td>Low</td>
<td>Not specified</td>
</tr>
<tr>
<td>Hermigier and鸡蛋, 7</td>
<td>8</td>
<td>Tubular with little or no tubulopapillary or papillary component</td>
<td>Low</td>
<td>Not specified</td>
</tr>
<tr>
<td>Tsuruma et al, 9</td>
<td>1</td>
<td>Papillary</td>
<td>Low</td>
<td>Not specified</td>
</tr>
<tr>
<td>Muller et al, 10</td>
<td>12</td>
<td>Tubular and tubulocystic</td>
<td>Low</td>
<td>Not seen</td>
</tr>
<tr>
<td>Current case</td>
<td>1</td>
<td>Tubular and tubulocystic</td>
<td>Low</td>
<td>absent</td>
</tr>
</tbody>
</table>

Figure 4

CD16  | Dallas, Carpentaria, CA | 32764 | 1:100 | negative in transverse |
CD26  | Dallas, Carpentaria, CA | 32764 | 1:100 | negative in transverse |
Smooth muscle myosin | Dallas, Carpentaria, CA | 1a4  | 1:200 | negative in transverse |
Carbonic anhydrase  | Dallas, Carpentaria, CA | A-287 | 1:200 | negative |
HMBS  | Dallas, Carpentaria, CA | HMBS4 | 1:400 | negative |

Figure 5

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### Figure 6

<table>
<thead>
<tr>
<th>Immuno-histochemical profile</th>
<th>Histology</th>
<th>EM</th>
<th>Patient outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not performed</td>
<td>PAS+</td>
<td>Brush borders - Mitochondria - Lateral infoldings -</td>
<td>Alive at time of writing</td>
</tr>
<tr>
<td>Not performed</td>
<td>Not specified</td>
<td>Slight microvilli, tight junctions with desmosomes, ZIP, free ribosomes and rough endoplasmic reticulum</td>
<td>NED for 5 years</td>
</tr>
<tr>
<td>CK7+</td>
<td>Mucinase -</td>
<td>Not described</td>
<td>NED 1-2 years later</td>
</tr>
<tr>
<td>HMWK+</td>
<td>Not specified</td>
<td>Not specifically delineated</td>
<td>Only patient with desmoplastic stroma died of disease</td>
</tr>
<tr>
<td>LMWK+</td>
<td>PNA+</td>
<td>HAE in 12/3</td>
<td>NED 1 year later</td>
</tr>
<tr>
<td>EMA+</td>
<td>Vimentin -</td>
<td>AHA in 1/2</td>
<td>94.1 NED</td>
</tr>
<tr>
<td>PNA+</td>
<td>HMWK+</td>
<td>Mucinase -</td>
<td>11.1 died of disease</td>
</tr>
<tr>
<td>PNA+</td>
<td>UEA-1+</td>
<td>H&amp;E colloidal iron deposit, PAS+, HMWK+</td>
<td>11.1 died of intercurrent disease</td>
</tr>
</tbody>
</table>

Abbreviations for Table 2

- CK7=Cytokeratin
- EMA=Epithelial membrane antigen
- HMWK=High molecular weight keratin
- LMWK=Low molecular weight keratin

* Case presented by O'Brien et al represents more of a renal pelvic epithelial tumor than a collecting duct carcinoma

Briefly, the tumor cells stained positively for epithelial membrane antigen (EMA), pan-cytokeratin, cytokeratins 8 and 18, cytokeratin 7, peanut agglutinin (PNA), Ulex europaeus-1 agglutinin (UEA-1), and vimentin. Staining was negative for RCC, CD10, high molecular weight cytokeratin (see table 1 and discussion), CD31, CD34, carcinoembryonic antigen (CEA), and HMB45. Immunohistochemical staining patterns of the tumor are depicted in figure 3.

### Figure 8

Figure 3A. Strong luminal staining of tumor tubules by peanut agglutinin (200X). Figure 3B. Cytoplasmic staining of tumor cells by Ulex europaeus lectin. The staining, however, is not as intense as is the endothelium of adjacent capillaries (200X). Figure 3C. Intense cytoplasmic staining of tumor cells for epithelial membrane antigen, with luminal accentuation (100X). Figure 3D. Staining for cytokeratin 7 is intense, but patchy, in tumor cell cytoplasm (100X).

Electron microscopy, performed on paraffin-embedded tumor tissue, revealed luminal surfaces with microvilli and well-developed desmosomes and tonofilaments, but no mitochondria.

The non-neoplastic renal parenchyma showed mild arterial and arteriolar sclerosis with less than 5% glomerular obsolescence and mild, focal interstitial fibrosis/tubular
atrophy. There was a concretion adjacent to one papilla, composed of both calcium phosphate and oxalate. There were also a few gouty tophi present within the deep medulla.

**DISCUSSION**

Collecting duct carcinoma (CDC) of the kidney was established as a distinct entity in 1986 by Fleming and Lewi, who defined it as a medially located, highly aggressive tumor with mixed solid and tubulopapillary patterns and an infiltrating tubular component eliciting a marked desmoplastic reaction. This type of renal carcinoma became characterized as an aggressive tumor, often presenting clinically with hematuria, symptoms related to an abdominal mass or even distant metastases. Originating in the renal medulla and secondarily extending into the cortex, CDCs are generally regarded as high-grade neoplasms expressing phenotypic markers of the normal collecting duct. The most specific of these include Ulex europaeus-1 lectin (UEA-1), peanut agglutinin (PNA) and high molecular weight cytokeratin (HMWK, 34+E12), and CDCs have been reported to show Periodic Acid Schiff (PAS) and variable mucin positivity (with either alcian blue or mucicarmine stains). Electron microscopy of CDCs reveals intra- and/or extracellular lumina, tight junctions and basal laminae. Tonofilament-like collections of intermediate filaments may be present and some lateral border complex infolding may be seen.

Chromosomal analysis has revealed that CDCs often show loss heterozygosity (LOH) of chromosome arm 1q, with LOH of 6p, 8p and 21q also observed. However, LOH of 3p, characteristic of proximal renal cancers, is infrequent in CDCs. Steiner et al have pinpointed the region of minimal deletion on chromosome arm 1q (located at 1q32.1-32.2) by high-density mapping and have found LOH in 69% of the 13 CDCs which they studied.

In recent years, there have been several reports describing low-grade renal carcinomas of putative collecting duct origin. Ironically, the first such case was that of Cromie, reported 7 years prior to the definitive description of CDC’s by Fleming and Lewi. Most such tumors were characterized by a benign follow-up course. All of these cases are outlined in table 2. The case presented herein shares a number of features with the previously reported low grade CDC cases cited above. It was centrally located and solid, composed of well-differentiated tubules lined by clear cells of low nuclear grade and it lacked a papillary component. It stained for collecting duct/distal nephron markers and conferred an (as yet) benign clinical course. While dysplastic changes were not seen in cells of adjacent collecting ducts, they were either not seen or not mentioned in the previously reported cases. The currently presented case, moreover, represents one of only a minority of putative low grade CDC’s to be described ultrastructurally (and the only one with no papillary component).

Unfortunately, none of the reported cases of low-grade carcinoma of putative collecting duct origin, including the presently reported case, were tested for deletions involving chromosomes 1 or 3. Nevertheless, the phenotypic expression of distal nephron/collecting duct epithelial markers and lack of proximal nephron markers in the present case are irrefutable. Specifically, the presently reported tumor expressed EMA, CAM 5.2, CK7, PNA and UEA-1, which are all markers of distal nephron/collecting ducts (See figure 3). While the presently reported case failed to stain for HMWK, the non-neoplastic collecting ducts in the adjacent medullary tissue likewise failed to stain for this marker (despite strong staining of the basal cell layer in normal prostatic glandular tissue, used as a positive control). The proximal tubular epithelial markers, RCC, CD10 and CD15, also positive in conventional renal cell carcinoma, were not expressed by the currently described tumor.

While chromophobe carcinoma might initially enter into the differential diagnosis, it can be easily ruled out as chromophobe carcinomas are vimentin negative and show diffuse reticular staining for Hale’s colloidal iron.

Thus, a diagnosis of low grade CDC might well be considered when the pathologist is confronted with an apparent conventional clear cell carcinoma that presents atypical features (i.e. non-cortical location, aberrant gross characteristics).

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