Renal Cell Carcinoma With Intratumoral Calcium Oxalate Crystal Deposition in Patients With Acquired Cystic Disease of the Kidney

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We describe 2 cases of renal cell carcinoma arising in acquired cystic disease of the kidney (ACDK) in patients with end-stage renal disease undergoing hemodialysis for more than 5 years and provide a brief review of the complications of ACDK. In both cases, abundant calcium oxalate crystals were observed within the tumors. Histologically, one of the tumors was a conventional (clear cell) renal cell carcinoma. The other tumor was a bilateral papillary renal cell carcinoma. Both tumors were high-grade carcinomas with extensive oncotic (acidophilic) features. Also noted within the kidneys were cysts with atypical papillary hyperplasia. The clinicopathologic findings along with review of the literature suggest a relationship between tumor growth and calcium oxalate crystal deposition in patients undergoing hemodialysis with ACDK.

(Arch Pathol Lab Med. 2003;127:e89–e92)

Acquired cystic disease of the kidney (ACDK) is commonly observed in patients with end-stage renal disease undergoing hemodialysis.1–3 One of the major complications of ACDK is neoplastic transformation.1 Other lesions in ACDK include deposits of oxalate, calcium, and immune complexes.5–7 We describe 2 cases of renal cell carcinomas with numerous calcium oxalate deposits, arising in ACDK, following long-term hemodialysis. To our knowledge, calcium oxalate crystals have been described previously in only 2 cases of unilateral papillary renal cell carcinoma in the context of ACDK.6 We are the first to report calcium oxalate crystal deposits in a conventional renal cell carcinoma and in bilateral papillary renal cell carcinoma arising in ACDK.

REPORT OF CASES

Case 1

Clinical History.—A 41-year-old African American man who had been undergoing hemodialysis for 10 years presented with end-stage renal disease likely secondary to hypertension. In 1997, he was noted incidentally to have multiple bilateral renal cysts. Computed tomography scan revealed a suspicious mass in the left kidney and a complicated cyst with a pedunculated mass protruding into a cyst in the right kidney. The patient underwent bilateral nephrectomy in 1997. A diagnosis was made of bilateral papillary renal cell carcinoma, nuclear grade III, arising in acquired cystic disease following hemodialysis. Four years later, the patient has no evidence of metastases or disease progression.

Pathologic Findings.—Grossly, the right and the left kidneys were remarkably similar and measured 11.5 × 6.8 × 3.1 cm and 11 × 8 × 6 cm, respectively. The right kidney contained a 4-cm, brown-gold cystic mass with papillary projections in the midteral kidney. Multiple other small simple cysts were seen throughout the kidney parenchyma. The left kidney appeared multicystic, with a 3.7-cm, yellow mass located in the lower pole of the kidney, associated with several small hemorrhagic areas.

Microscopically, both tumors were high-grade papillary renal cell carcinomas (Fuhrman nuclear grade 3/4) and were organ confined (Figure 1, A). Tumor cells had darkly acidophilic cytoplasm with oncotic features. Deposits of hemosiderin and areas of recent hemorrhagic were noted. Large quantities of calcium oxalate crystals were found within both tumors. Calcium oxalate crystals were clear to slightly opaque, polymorphic, and polarizable (Figure 1, B). The tumors arose in typical ACDK with end-stage renal disease. Several cysts in both kidneys revealed papillary hyperplasia characterized by a single layer of cuboidal cells with eosinophilic cytoplasm and bland cytologic features that covered thin fibrovascular papillary stalks. Focally, the cyst linings were atypical with nuclear enlargement and hyperchromasia (Figure 2). Calcium oxalate crystals were also identified outside the tumor to a much lesser extent.

Case 2

Clinical History.—A 46-year-old white woman with a long history of systemic lupus erythematosus, hypertension, and hepatitis C had end-stage renal disease for which she had been treated with hemodialysis for 6 years. In 2001, a renal mass was discovered incidentally during a workup for gallbladder disease, and the patient underwent a left nephrectomy. A diagnosis of renal cell carcinoma with oncotic features, nuclear grade 3, arising in ACDK was made.

Pathologic Findings—The left kidney consisted of a 10 × 6-cm radical nephrectomy specimen. The kidney was composed almost completely of multiple multiloculated cysts, ranging from 0.3 to 4 cm in diameter. Within the cyst located over the superior and middle poles of the specimen was a 5 × 2.5 × 2-cm, yellow-orange, well-circumscribed mass, which was confined to the cyst. The tumor was a conventional renal cell carcinoma, nuclear grade 3/4. Cells were arranged in sheets or alveoli and dilated cystic tubules, demarcated by foci of interconnecting capillary and sinusoidal structures. Tumor cells had abundant acidophilic cytoplasm (Figure 3, A). Numerous and dispersed calcium oxalate crystals were present within the tumor (Figure 3, B). The tumor was organ confined. The background revealed changes of end-stage kidney disease. In the surrounding kidney, cysts were
Figure 1. Case 1. A, High-grade papillary renal cell carcinoma with calcifications arising in acquired cystic disease of the kidney (hematoxylin-eosin, original magnification ×20). B, Multiple calcium oxalate crystal deposition in papillary renal cell carcinoma with oncocytic (acidophilic) features (hematoxylin-eosin, original magnification ×40).

Figure 2. Case 1. Atypical papillary hyperplasia arising in a cyst in a context of acquired cystic disease of the kidney (hematoxylin-eosin, original magnification ×20).

Figure 3. Case 2. A, Low magnification of a conventional renal cell carcinoma (bottom) with areas of cystic tubule formation (top) (hematoxylin-eosin, original magnification ×4). B, Extensive oncocytic features of conventional renal cell carcinoma containing numerous clear to slightly opaque calcium oxalate crystals (hematoxylin-eosin, original magnification ×40).
variably sized and mostly lined by a single flattened, cuboidal, or partially denuded benign-appearing epithelium. Calcium oxalate crystals were identified outside the tumor, yet to a much lesser extent. Multilayered epithelial cells with granular eosinophilic or clear cytoplasm, focally with papillary features and mild atypia, lined some cysts.

**COMMENT**

Dunnill et al. were the first to report ACDK as an effect of end-stage renal disease, generally in patients undergoing hemodialysis. The condition was characterized by 1- to 2-cm cysts distributed randomly throughout the cortex and medulla of the kidney. It is generally accepted that more than 3 cysts should be present or more than 25% of the kidney should be involved and a history of polycystic kidney disease should be absent. The incidence of ACDK in patients with end-stage renal disease ranges from 30% to 95%. The duration of maintenance dialysis is the most strongly associated risk factor. Approximately 8% of the patients with end-stage renal disease have ACDK at the initiation of dialysis. After 1 to 3 years of dialysis, 10% to 20% of patients have ACDK. This rate increases to 40% to 60% at 3 to 5 years of dialysis and up to 90% after 5 to 10 years of dialysis.

The main complication in ACDK is the increased risk of developing renal tumors, where the incidence is 12 to 18 times higher than that in the general population and which occurs 20 years earlier than in the general population. Renal tumors included benign and malignant neoplasms and have been reported in 20% to 33% of patients with ACDK. Most of the renal tumors arising in ACDK are benign and correspond to papillary adenomas or oncocytoma. Other tumors and tumorlike conditions that have been described include angiomylipoma, papillary hyperplasia of the cyst epithelium, and atypical epithelial hyperplasia. Eighteen percent of the tumors arising in ACDK are renal cell carcinoma, seen in approximately 6% of ACDK in long-term dialysis patients. According to several studies, tumor transformation in ACDK occurs more frequently with longer duration of hemodialysis. The main tumor types described in the literature are papillary or conventional (clear cell type) renal cell carcinoma. The cytogenetic changes of the papillary subtype associated with ACDK are similar to those seen in tumors without ACDK. Tumors in ACDK are frequently multifocal (50%) and usually less than 3 cm in diameter. The frequency of bilateral tumors in ACDK is unknown, in part due to sporadic case reports and small pathological series. To our knowledge, we are the third series with a bilateral tumor arising in ACDK. Usually, renal cell carcinoma arising in ACDK is considered to be a tumor of low malignant potential compared with classic renal cell carcinoma. However, 6% to 27% of renal cell carcinomas arising from ACDK have been reported to metastasize. Rare cases of renal cell carcinoma with a sarcomatoid component have also been described; all had a fatal outcome, with death occurring 2 years following the renal tumor diagnosis.

Although the cell of origin of ACDK and tumor transformation remains unknown, chemical analysis of cyst fluid and ultrastructural analysis implicate the proximal tubule. Theories regarding the pathogenesis of ACDK and secondary tumor development include in part toxins related to hemodialysis, accumulation of mutagenic or carcinogenic uremic metabolites, immunosuppression, effect of renotropic growth factor, renal tubular obstruction resulting from interstitial fibrosis, deposition of calcium oxalate and immune complex in the tubular lumina, focal proliferation of renal tubular epithelium, and alteration in tubular basement membrane. Several authors have noted that many of the cysts in ACDK are lined by hyperplastic multilayered epithelium with papillary projections from which papillary carcinoma may arise. McManus et al. showed increased proliferative activity in both glomerular and tubular epithelium, which could explain the large variety of epithelial neoplasms observed in dialysis patients with ACDK.

Oxalosis is a characteristic feature of kidneys with end-stage disease and has been implicated in the pathogenesis of ACDK with tumor transformation. There are more than 100 cases of ACDK with tumor in the literature, but only one study reported 2 cases of papillary renal cell carcinoma with extensive tumor calcium oxalate deposits in ACDK. We report the first case of calcium oxalate crystals in a bilateral papillary renal cell carcinoma and in a conventional (clear cell type) renal cell carcinoma arising in ACDK. Interestingly, all the tumors in our series showed extensive oncocytic (acidophilic) features that were mentioned in one previous study. In the other study describing renal cell carcinoma with ACDK and oxalosis, oncocytic features were not mentioned. However, the only illustration of their tumor shows oncocytic cytoplasm. An analysis of additional cases is required to determine whether oncocytic features appear to be characteristic of renal cell carcinoma arising in ACDK.

Calcium oxalate crystals have previously been described in end-stage renal disease in the walls of ACDK. Pre-existing crystals may become incorporated secondarily during neoplastic transformation. Other types of calcifications, such as psammomatous calcifications and ossification, have also been reported. Several authors have studied nephrocalcin, an acidic glycoprotein that inhibits growth, aggregation, and secondary nucleation of calcium oxalate monohydrate crystals. Nephrocalcin is produced by renal proximal tubule cells but has been also localized to cells of primary renal cell carcinoma. Consistent with finding calcium oxalate in the tumors in our study, nephrocalcin has been described as decreased in renal cell carcinoma in patients undergoing long-term hemodialysis. Another hypothesis that could explain the relation between tumor transformation and oxalosis is cyst and eventual tumor formation arising as a complication of tubular obstruction by calcium oxalate crystal.

This phenomenon appears relatively rare in the United States based on the literature and an informal survey of several leaders in urological pathology from this country who have published extensively on renal cell carcinoma (J. N. Eble, V. R. Reuter, M. B. Amin, and R. H. Young, written communication, 2002). However, the finding of calcium oxalate crystals in renal tumors in patients undergoing long-term dialysis does not appear to be as uncommon in Japan, where renal transplantation is rare (Toyonori Tsuzuki, written communication, 2002). The finding of numerous calcium oxalate crystals in renal cell carcinoma may be directly related to time undergoing dialysis. We hope the current study will stimulate additional information on this topic from this and other countries.

**References**