Renal Cell Carcinoma in Autosomal Dominant Polycystic Kidney Disease

Douglas S. Keith, Vicente E. Torres, Bernard F. King, Horst Zincki, and George M. Farrow

D.S. Keith, V.E. Torres, Division of Internal Medicine and Nephrology, Mayo Clinic and Foundation, Rochester, MN
B.F. King, Department of Diagnostic Radiology, Mayo Clinic and Foundation, Rochester, MN
H. Zincki, Department of Urology, Mayo Clinic and Foundation, Rochester, MN
G.M. Farrow, Division of Laboratory Medicine and Pathology, Mayo Clinic and Foundation, Rochester, MN

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ABSTRACT
To provide information on the clinical presentation, diagnosis, pathology, and biologic behavior of renal cell carcinoma in patients with autosomal dominant polycystic kidney disease (ADPKD), three cases seen at this institution between 1955 and 1992, as well as the cases reported in the literature, were reviewed in detail. No male predominance was observed (12 men, 13 women) in the 25 patients who met the inclusion criteria. The age of presentation was earlier than that seen in the general population (45 versus 61 yr). Fever, night sweats, and weight loss were prominent at presentation. Fever is a more common presenting symptom of renal cell carcinoma in ADPKD (32%) than in the general population (7%). Twenty percent of the patients had metastatic disease at presentation. Even with computed tomography and magnetic resonance, the diagnosis was difficult and often delayed, and the accumulation of 111In-labeled white blood cells can wrongly suggest a cyst infection. Renal cell carcinoma in ADPKD is more often concurrently bilateral (12 versus 1 to 5%), multicentric (28 versus 6%), and sarcomatoid in type (33 versus 1 to 5%) than in the general population. Because previous studies have failed to demonstrate a higher prevalence of renal cell carcinoma in ADPKD, this information suggests either a malignant potential restricted to a small subset of patients with this disease or an alteration in the biologic behavior of renal cell carcinoma when it develops in the setting of ADPKD.

Key Words: Polycystic kidney disease, renal cell carcinoma, sarcomatoid renal cell carcinoma

The association of renal cell carcinoma (RCC) and autosomal dominant polycystic kidney disease (ADPKD) remains controversial. Numerous case reports of ADPKD complicated by RCC have been described (1-26), and pathologic studies of polycystic kidneys have shown that potentially premalignant cellular hyperplasia of the cyst epithelia occurs frequently in ADPKD (27-29). On the other hand, epidemiologic and autopsy studies have not shown a higher incidence of RCC in ADPKD, although the studies are small (30,31). This article reviews three cases of ADPKD with RCC seen at our institution as well as reviews the literature on this topic. The biologic behavior, clinical presentation, pathology, and potential difficulties in the diagnosis of RCC in this setting will be discussed, including the role of computed tomography (CT) and magnetic resonance (MR) scans.

PATIENTS AND METHODS
Between 1955 and 1992, all cases of ADPKD and RCC were identified by use of the Mayo medical records system. Criteria for inclusion in the study included a clinical diagnosis of ADPKD and RCC, as well as histologic confirmation of RCC. The criteria for a diagnosis of ADPKD included bilateral enlargement and cystic transformation of the kidneys and exclusion of other renal cystic diseases such as von Hippel-Lindau disease, tuberous sclerosis complex, or acquired cystic disease of renal failure. Immunohistochemistry, cytogenetics, and chromosomal ploidy were obtained on the tumor tissue when possible.

All relevant English, French, Spanish, and German language articles were identified through Medline Search, and references were selected from bibliographies of identified articles. To be included in this review, cases required clearly documented evidence of bilateral polycystic kidneys by imaging, autopsy, or surgery, with the exclusion of other renal cystic diseases. All cases required histologically proven RCC. Other tumor types, such as angiomylipomas or sarcomas, were excluded. In some references, the
TABLE 1. Summary of ADPKD cases complicated by RCC at our institution

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Presentation (yr)</td>
<td>31</td>
<td>44</td>
<td>62</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Family History of ADPKD</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Signs and Symptoms</td>
<td>None</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Hematuria</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Flank pain</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Elevated LFT</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Other Unilateral versus Bilateral Pathology</td>
<td>Anemia... Unilateral Grade 3</td>
<td>RCC, clear... Carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unilateral Grade 2</td>
<td>RCC, clear... Sarcoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unilateral Grade 4</td>
<td>RCC, clear... Coma-foid</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Died</td>
<td>Died</td>
<td>Died</td>
</tr>
</tbody>
</table>

LFT, liver function tests; Pul. Mts., pulmonary metastasis.

Individual case histories were not given, and these cases were also excluded from the analysis. Data regarding presentation, pathology, and course were obtained when possible from these reports and were used to review the features of RCC in ADPKD (Table 1).

CASE REPORTS

Patient 1

A 31-year-old man with known ADPKD presented to our institution with left flank pain, gross hematuria, malaise, weight loss of 10 lbs, and fever of unknown origin for the last 5 mo. He had no family history of ADPKD. His mother died of breast cancer; otherwise there was no family history of cancer. He was a smoker. His serum creatinine was 1.2 mg/dL. Extensive testing including an IV pyelogram, and a lymphangiogram was unrevealing.

Three months later, the patient returned for persistent fevers in spite of treatment with antibiotics. A visceral angiogram revealed a large, vascular RCC in the left polycystic kidney (Figure 1A). He underwent a left radical nephrectomy. The kidney measured 20 × 8 × 6 cm, and the entire non-neoplastic parenchyma was totally replaced by multiple cysts, ranging in size from 0.3 up to 2.5 cm in greatest diameter. Situated in the midportion of the kidney, there was a circumscribed nodular mass of RCC that measured 7 × 6 × 5 cm (Figure 1B). The tumor compressed the surface of the renal pelvis and collecting system but did not invade it. It did not extend beyond the renal capsule, and the renal vessels were not involved. Histologically, the tumor was a nuclear Grade 3 RCC, predominantly of clear cell type, but with mixed granular cell elements. DNA flow cytometry of the tumor tissue revealed a tetraploid pattern. Cytogenetics were not performed.

The patient remained disease free until 5 yr after the nephrectomy when a lung mass was noted on chest x-ray. A biopsy revealed metastatic RCC. The patient died 15 mo later of metastatic disease.

Patient 2

A 44-year-old woman with known ADPKD presented to our institution with an 8-mo history of increasing abdominal girth, malaise, left flank pain, and weight loss of 5 lbs. In the last 3 mo, she had developed low-grade fevers and anemia requiring the transfusion of 10 U of blood. Two months before presentation, a CT scan of the abdomen revealed a huge, left renal cyst extending into the pelvis, as well as a poorly defined mass inside the left kidney. The large left renal cyst was aspirated. The fluid was clear and noninfected and had a nonmalignant cytology. She denied any recent history of gross hematuria.

She was a nonsmoker. Her family history was remarkable for ADPKD in her brother. Her mother died of multiple myeloma. A review of the autopsy revealed that she also had ADPKD. On examination, the patient was emaciated with a height of 165 cm
and a weight of 54.7 kg. Her blood pressure was 130/80 with a pulse of 105, and she was afebrile. A large mass occupied the whole left side of the abdomen. The liver could be felt two fingerbreadths below the right costal margin. There was a 1-cm lymph node noted in each axilla.

Laboratory examination revealed a normocytic anemia with a hemoglobin at 10.6 g/dL. Platelet and white blood cell counts were normal. Her serum creatinine was 0.8 mg/dL. Urinalysis showed microhematuria and trace proteinuria. Her serum alkaline phosphatase was elevated at 543 U/L with fractionation showing the liver fraction to be elevated.

A CT scan of the abdomen demonstrated a large necrotic tumor in the left polycystic kidney (Figure 2). The collecting system was markedly distorted and splayed. Numerous cysts were seen in the kidneys and liver. A large, 10-cm cyst arising from the lower pole of the left kidney extended into the pelvis and compressed the bladder. An MR scan of the abdomen revealed a large mass with a necrotic center arising from the left kidney. Inferior to the mass, there was a large cyst extending down to the pelvis (Figure 3A). A moderate-sized tumor thrombus extended to the level of the left renal vein (Figure 3B).

The patient underwent a left radical nephrectomy. The kidney measured 23 × 15 × 10 cm. The renal cortex was totally replaced by innumerable cysts ranging in size from 0.3 up to 3.5 cm in greatest diameter. In the central portion of the kidney, there was an RCC that measured 6 × 4 × 4 cm. The tumor was a clear cell renal carcinoma, nuclear Grade 2. Multiple periaortic lymph nodes were negative for

Figure 2. (A) CT scan through the liver and left kidney demonstrating polycystic liver and kidney disease. (B) CT scan with iv contrast of the same patient through the midportions of both kidneys. Large necrotic irregular mass (arrowsheads) in the left kidney.

Figure 3. (A) Sagittal T1-weighted (TR, 550 ms; TE, 11 ms) MR image with fat saturation and gadolinium enhancement of the left kidney demonstrating a large, central, necrotic RCC (white arrows). A large cyst (black arrows) arising from the lower pole of the left kidney extends into the pelvis. (B) Transverse T1-weighted (TR, 600 ms; TE, 12 ms) image with fat saturation and gadolinium enhancement of the left kidney and liver demonstrating a tumor thrombus (open arrow) in the left renal vein.
neoplasm. DNA flow cytometry of the tumor revealed an aneuploid pattern. The cytogenetic karyotype was 46 xx in 29 cells and 46 xx, del (6) (q15, q25) in one cell.

Two months after her nephrectomy, two right pulmonary nodules were found. Wedge resection revealed RCC. The patient is alive 2 yr later.

Patient 3
A 62-year-old woman with a history of breast cancer treated with mastectomy, cytoxan, 5-fluorouracil, and prednisone 15 yr earlier presented with a 3-wk history of nausea, anorexia, and flank pain. She had a family history of ADPKD but no family history of cancer. She was a nonsmoker.

The initial CT scan of the abdomen revealed bilateral polycystic kidneys, liver cysts, and small bilateral renal stones (Figure 4A). A urine culture was negative. The serum creatinine was 1.2 mg/dL. After the initial evaluation, the patient noted daily fevers to 38°C, fatigue, dysgeusia, and anorexia. Ciprofloxacin, 500 mg twice daily, was started. Repeat urine and blood cultures were negative. An indium white blood cell scan showed a faintly increased uptake in the left kidney. Three weeks later, gross hematuria developed and flank pain, malaise, and anorexia persisted. New leukocytosis, anemia, and elevated erythrocyte sedimentation rate were detected. An MR scan of the abdomen 3 wk after the initial CT scan showed a few hemorrhagic cysts in the left kidney and nor-

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Figure 4. (A) CT scan with iv contrast through both kidneys and liver demonstrating polycystic kidney and liver disease. (B) Transverse T1-weighted (TR, 550 ms; TE, 12 ms) MR image obtained 3 wk later through both kidneys and liver demonstrating polycystic kidney and liver disease. Note a small hemorrhagic cyst (arrow) in the left kidney and small normal-sized lymph nodes (arrowhead) in the left periaortic region. (C) CT scan with iv contrast through both kidneys and liver obtained 7 wk after the initial CT scan. Irregular, ill-defined cystic areas (open arrows) in the medial aspect of the left kidney have significantly changed since the initial CT scan. Note the interval enlargement of the left periaortic lymph nodes (arrowhead). (D) Transverse, T1-weighted (TR, 500 ms; TE, 11 ms) MR image through both kidneys and liver 9 wk after the initial CT scan. Note the ill-defined soft tissue mass (open arrows) in the medial aspect of the left kidney and the rapid increase in the size of the left periaortic lymph nodes (arrowhead).
mal-sized periaortic lymph nodes (Figure 4B). She continued to feel ill, and a weight loss of 20 lbs was noted. A CT scan of the abdomen 7 wk after the initial CT showed ill-defined cystic areas in the medial aspect of the left kidney and enlargement of the periaortic lymph nodes (Figure 4C). A third urine culture revealed infection with ≥10⁵ Staphylococcus aureus organisms/mL, which was treated with IV nafcillin. A repeat MR scan 2 wk later showed a poorly defined soft tissue density in the left renal hilum extending into the left retroperitoneum and a rapid increase in the size of the periaortic adenopathy (Figure 4D). A CT-guided biopsy of the left retroperitoneal mass showed a neoplasm, nuclear Grade 4, with prominent necrosis and sarcomatoid features. By immunohistochemistry, the tumor exhibited intense cytoplasmic immunoreactivity for keratin AE1/AE3 and CAM 5.2, with negative staining for leukocyte common antigen and S-100 protein. Vimentin immunostain showed variable reactivity. A periodic acid-Schiff stain revealed moderate glycogen within the tumor cells. The interpretation was that of sarcomatoid RCC, Grade 4. No DNA flow cytometry or cytogenetics were obtained.

The patient was started on megace. She developed multiple pulmonary metastasis, and the megace was stopped. She died from carcinomatosis 2 mo after the diagnosis of her tumor.

REVIEW OF PUBLISHED CASE REPORTS

Thirty cases of ADPKD and RCC were identified in the literature (1–26). Seven cases had no accompanying history and were excluded from the review (24,25). Another case was excluded because the description of the tumors was more compatible with a diagnosis of cortical adenomas than with that of RCC (26).

A summary of the remaining 22 cases is shown in Table 2. The mean age at diagnosis of RCC was 47 yr. Eleven of the 22 patients were men. Fourteen of the 22 case histories commented on family history of ADPKD. Only 8 of the 14 cases reported positive family histories for ADPKD (7) or for renal failure (1). Two patients were felt likely to have ADPKD despite a vague family history of brain or intracranial tumors and were included in the review (4,5,18). Three of the patients had bilateral tumors at the time of di-

<table>
<thead>
<tr>
<th>Author (Ref. No.)</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Family History of ADPKD</th>
<th>Location</th>
<th>Pathologic Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Der Vuurst De Vries (1)</td>
<td>38</td>
<td>M</td>
<td>-</td>
<td>U</td>
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</tr>
<tr>
<td>Melicow and Glie (2)</td>
<td>64</td>
<td>M</td>
<td>NA</td>
<td>U</td>
<td>-</td>
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<td>Bobbitt (3)</td>
<td>46</td>
<td>M</td>
<td>NA</td>
<td>U</td>
<td>-</td>
</tr>
<tr>
<td>Lewis, Kimbrough, and Borski (4, 5)</td>
<td>39</td>
<td>M</td>
<td>-</td>
<td>BAS</td>
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<td>Dalgaard (6)</td>
<td>37</td>
<td>M</td>
<td>NA</td>
<td>U</td>
<td>-</td>
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<tr>
<td>Brannan et al. (7)</td>
<td>65</td>
<td>F</td>
<td>NA</td>
<td>U</td>
<td>-</td>
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<tr>
<td>Howard and Young (8)</td>
<td>32</td>
<td>F</td>
<td>+</td>
<td>U, MC</td>
<td>-</td>
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<td>McFarland et al. (9)</td>
<td>45</td>
<td>F</td>
<td>NA</td>
<td>U</td>
<td>-</td>
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<tr>
<td>Roberts (10) and Wright et al. (11)</td>
<td>44</td>
<td>M</td>
<td>+</td>
<td>BS, MC</td>
<td>Synchronous clear cell, sarcomatoid type tumors</td>
</tr>
<tr>
<td>Regan et al. (12)</td>
<td>39</td>
<td>M</td>
<td>+</td>
<td>U</td>
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<tr>
<td>Regan et al. (12)</td>
<td>47</td>
<td>F</td>
<td>+</td>
<td>U</td>
<td>-</td>
</tr>
<tr>
<td>Tan et al. (13)</td>
<td>62</td>
<td>M</td>
<td>NA</td>
<td>U, MC</td>
<td>Clear cell type</td>
</tr>
<tr>
<td>Tegtmeyer et al. (14)</td>
<td>29</td>
<td>F</td>
<td>NA</td>
<td>U</td>
<td>-</td>
</tr>
<tr>
<td>Tegtmeyer et al. (14)</td>
<td>39</td>
<td>F</td>
<td>+</td>
<td>BS, MC</td>
<td>-</td>
</tr>
<tr>
<td>Kumar et al. (15)</td>
<td>31</td>
<td>F</td>
<td>-</td>
<td>U</td>
<td>Sarcomatoid type</td>
</tr>
<tr>
<td>Oe et al. (16)</td>
<td>67</td>
<td>F</td>
<td>-</td>
<td>U</td>
<td>Clear cell type</td>
</tr>
<tr>
<td>Ng and Suki (17)</td>
<td>46</td>
<td>M</td>
<td>+</td>
<td>U, MC</td>
<td>-</td>
</tr>
<tr>
<td>Sogbein et al. (18)</td>
<td>40</td>
<td>M</td>
<td>-</td>
<td>BAS, MC</td>
<td>-</td>
</tr>
<tr>
<td>Lee et al. (19)</td>
<td>65</td>
<td>F</td>
<td>NA</td>
<td>U</td>
<td>Sarcomatoid type</td>
</tr>
<tr>
<td>Kallit and Sellami (20)</td>
<td>61</td>
<td>F</td>
<td>+</td>
<td>BS, MC</td>
<td>Clear cell type</td>
</tr>
<tr>
<td>Blech (21)</td>
<td>49</td>
<td>F</td>
<td>+</td>
<td>U</td>
<td>-</td>
</tr>
<tr>
<td>Saragnano et al. (22)</td>
<td>59</td>
<td>M</td>
<td>-</td>
<td>U</td>
<td>-</td>
</tr>
</tbody>
</table>

* U, unilateral; BS, bilateral synchronous; BAS, bilateral asynchronous; MC, multicentric; +, positive; -, negative; NA, information not available.
agnosis (10,11,14). Two additional patients developed RCC in the contralateral kidney 3 and 6 yr after their initial surgery respectively (4,5,18). Seven patients had multicentric tumors (8,10,11,13,14,17,18,20). Of the 22 cases, only 9 reported the histologic subtype of the tumor. Six of the nine cases were clear cell type, two were sarcomatoid, and one patient had synchronous sarcomatoid and clear cell-type carcinomas. Four patients presented with tumors after their ADPKD had reached end stage (12,16,17,19). Two of these patients had previously failed renal transplants (12,17). All four were receiving hemodialysis at the time of the diagnosis of their tumors.

**DISCUSSION**

The association of RCC and ADPKD remains controversial. Herein, we have described three cases of ADPKD complicated by RCC that have been identified at our institution. A fourth case with low-grade bilateral tubulopapillary and clear cell adenocarcinomas cited in a previous publication was omitted because the diagnosis of RCC was made at autopsy, there was no family history of ADPKD, the kidneys were only moderately enlarged (right, 375 g; left, 475 g), and the patient had been on dialysis for 5 wk (27). When our cases and the published cases were reviewed, several generalizations regarding RCC in ADPKD could be made.

First, the age at the time of presentation of RCC in ADPKD was earlier than that seen in the general population. The median age of the ADPKD patients with RCC was 45 yr, significantly lower than that of Olmsted County patients with RCC diagnosed during life (61 yr; \( P < 0.001 \)) or at autopsy (74 yr; \( P < 0.001 \)) (32). Before the development of chronic hemodialysis and renal transplantation, patients with ADPKD had a shorter life expectancy than people in the general population (6,33). This could skew the age of presentation downward because fewer patients with ADPKD would have lived into the seventh and eighth decades of life. In addition, there may be a reporting bias favoring the publication of RCC in younger patients. Nevertheless, well over half of the cases reported were in patients under the age of 50 yr, and it seems likely that this reflects a true difference in the behavior of RCC in ADPKD. In addition, the male predominance observed in unselected patients with RCC (approximately 2:1 (34,35) was not observed in this patient group (12 men, 13 women).

Although the clinical presentation of RCC in ADPKD was similar to that seen in the general population (Table 3) (36) several features appeared to be more prevalent in ADPKD. Flank pain and gross hematuria were the most common presenting symptoms, but often, fever, night sweats, and weight loss were also prominent at presentation. Fever was observed in 8 (32%) of 25 patients with ADPKD as compared with 7% in the general population (3,7,10,15,19). The triad of fever, flank pain, and weight loss was seen in all three patients from our institution. Symptoms or signs related to metastatic disease were present in 5 (20%) of 26 patients (9,10,11,16,20).

The diagnosis of RCC in ADPKD still presents a vexing problem for the clinician because symptoms such as fever, flank pain, and hematuria are frequently seen with other complications of this disease. Weight loss, if present, should highly increase the suspicion for the presence of RCC. Because of the difficulties inherent in the diagnosis of complications in ADPKD, the diagnosis of RCC may be delayed. An average of 6 mo elapsed between the onset of symptoms and the diagnosis of RCC in the patients seen at our institution, although these three patients had been extensively evaluated before the correct diagnosis was made.

Even with the improvements in CT and MR technologies, the diagnostic imaging of RCC in ADPKD may be difficult, as exemplified by Patients 2 and 3. This is so because the kidneys are replaced by multiple cysts that vary in size and appearance on various imaging studies. Some cysts can be complicated by hemorrhage, therefore giving an intermediate or high-density appearance on CT scans or a high-intensity appearance on MR scans. Similarly, cysts containing internal debris or hemorrhagic components may appear as complex or even solid on ultrasound. This is compounded by the fact that many RCC contain fairly large areas of cystic necrosis. CT without and after iv contrast material, with thin (5-mm) slices through areas of interest, is the primary imaging modality for the evaluation of patients with ADPKD who may have RCC. Particular attention should be made to previous CT studies in order that subtle changes in symmetry, parenchyma, or soft tissue density can be observed. Although periaortic adenopathy can occur with infections involving the kidneys, it should also suggest an occult RCC within

## Table 3. Presenting symptoms of RCC in ADPKD compared with the reported prevalence of symptoms of RCC in the general population (34)

| Symptom                       | RCC in ADPKD | General Population (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Flank Pain</td>
<td>12/25 (48%)</td>
<td>41</td>
</tr>
<tr>
<td>Hematuria</td>
<td>11/25 (44%)</td>
<td>59</td>
</tr>
<tr>
<td>Fever</td>
<td>8/25 (32%)</td>
<td>7</td>
</tr>
<tr>
<td>Symptoms of Metastatic Disease</td>
<td>5/25 (20%)</td>
<td>10</td>
</tr>
<tr>
<td>None</td>
<td>3/25 (12%)</td>
<td>7</td>
</tr>
</tbody>
</table>
the polycystic kidneys, as occurred in Patient 3. Enlarged renal veins may also be a subtle indicator of tumor thrombus within a renal vein in a kidney with occult renal neoplasm. A cyst with a thick, irregular wall should raise the possibility of a necrotic neoplasm. When iv contrast material cannot be given because of poor renal function or allergy, when the results of CT are inconclusive or when there is a suspicion of RCC despite a negative CT, further evaluation with MR without and with gadolinium enhancement should be performed. Many cysts in ADPKD contain various amounts of proteinaceous material and/or blood products, which cause different signal intensities on T1- and T2-weighted images. After the iv administration of gadolinium, however, the contrast between renal parenchyma and renal cysts becomes more dramatic, and it is easier to differentiate a normal or complicated cyst from a cystic or necrotic RCC. MR is also useful in evaluating the renal vein for patency and the inferior vena cava for the presence of tumor thrombus.

Radioactive indium-labeled white blood cell and gallium scans can be useful in identifying an infected cyst within a polycystic kidney or liver. As illustrated by Patient 3, a malignant tumor such as RCC can elicit an inflammatory response and in some cases causes the accumulation of gallium- or indium-labeled white blood cells in or around the tumor site. Therefore, the thought that neoplasm may mimic infection should be kept in mind in the evaluation of patients with ADPKD and a clinical presentation that suggests an infected cyst. With the availability of CT and MR, renal arteriography has a negligible role in the diagnosis of RCC in anatomically normal kidneys. The detection of a small RCC in a polycystic kidney, however, can elude sophisticated CT and MR examinations. It is unlikely that arteriography could help in rare cases where the suspicion of RCC remains high despite negative or inconclusive CT and MR examinations. Surgical exploration, open biopsy, or even nephrectomy may be needed to completely exclude the possibility of underlying malignant neoplasm.

Among the cases in our review where histologic subtypes were reported, there was a higher proportion of sarcomatoid tumors than has been reported in the general population. Four of 12 reported cases had sarcomatoid tumors (10,11,15,20). The reported proportion of RCC that are of the sarcomatoid variant in the general population is between 1 and 5% (37,38). This variant of RCC tends to be particularly aggressive, with a high metastatic rate and shortened survival (39). This is confirmed by the case from our institution and by the other three reported cases, all of which had an early death or metastatic disease.

In our review of the literature, concurrent bilateral and multicentric tumors appeared to be more prevalent than would be expected in the general population. The reported percentage of RCC that presents as concurrent bilateral disease is between 1 and 5% (40–42), whereas the percentage of asynchronous bilateral RCC has been reported to be as high as 13% in long-term follow-up with CT (43). In our review, 3 (12%) of the 25 cases were bilateral at the time of diagnosis, whereas 2 (8%) additional cases developed RCC in the contralateral kidney after the primary diagnosis. The incidence of multicentric RCC has been reported to be approximately 7% (44). In our review, 7 (28%) of 25 cases had multicentric tumors.

Ng and Suki have also reported a higher percentage of bilateral RCC in polycystic kidneys (20%) (17). They did not, however, specify whether these were synchronous or asynchronous occurrences, nor were their selection criteria for cases reported. The spurious inclusion of cases of von Hippel-Lindau disease would likely increase the percentage of bilateral tumors (63%) (45). Although the difference is small, our review of the literature, with specific exclusion of cases of von Hippel-Lindau syndrome, still supports their observation that ADPKD has a higher percentage of concurrent bilateral tumors.

Only four cases of RCC in ADPKD occurred in patients with ESRD. Dialysis has been shown to enhance renal epithelial proliferation in both ADPKD and non-ADPKD kidneys (27,46), and acquired cystic disease of renal failure has a higher incidence of renal tumors (47–49). Similarly, transplantation has been associated with a higher incidence of cancer, particularly lymphoma (50). Whether uremic ADPKD patients are at higher risk for the development of RCC is unclear. The majority of cases in this review were not uremic at the time of diagnosis, although one third of the cases were reported before 1970 when chronic hemodialysis was not widely available. Two of the patients reported had previous renal transplants; however, at the time of detection both were on hemodialysis. The long-term outcome of transplanted ADPKD patients from our institution detected no renal tumors in the 54 patients monitored for a mean of 3 yr (51). Others have reported no apparent increase in renal tumors in hemodialyzed ADPKD patients (52). Therefore, there is little evidence beyond theoretical considerations to support the contention that uremia or transplantation in ADPKD appreciably increases the risk of RCC beyond that seen in the dialysis and transplant population in general.

Although the behavior of RCC in ADPKD was different in several respects from that which has been observed in RCC in the general population, no clear evidence exists that ADPKD patients are at increased risk for RCC. The younger age of presentation, the increased percentage of concurrent bilateral and multicentric tumors, and the higher percentage of
sarcomatoid histology does not prove the contention that ADPKD is a positive risk factor for RCC. It may only indicate that when RCC occurs in ADPKD, it behaves differently than that seen in normal kidneys. Similarly, the many case reports in the literature do not prove the existence of an association because the chance association of two relatively common disorders would be expected in a considerable number of patients. Two studies of the incidence of RCC in ADPKD were unable to show a higher incidence of RCC than chance alone, although both studies were small (30,31). The possibility that this risk could be higher in a subset of patients with ADPKD cannot be excluded, but at present, no adequate means to identify these patients is available. Even if an increased risk of RCC exists, the risk is likely small and unlikely to change clinical practice. Until larger studies can be performed and more is learned about the pathogenesis of ADPKD and RCC, it seems reasonable to conclude that ADPKD is not a proven risk factor for RCC.

REFERENCES