Renal Cell Carcinoma in Transplant Recipients with Acquired Cystic Kidney Disease

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Background: Acquired cystic kidney disease (ACKD) is a widely known renal cell carcinoma risk factor. Design, setting, participants, and measurements: An ultrasound screening of the native kidneys in all renal transplant patients of a renal outpatient clinic who received a transplant between 1970 and 1998 and presented between 1997 and 2003 (n = 916) was initiated prospectively. A total of 561 patients were screened.

Results: A total of 129 (23%) patients had ACKD; 46 (8.2%) patients had complex renal cysts (Bosniak classification, category IIIF to III); and eight (1.5%) patients had newly diagnosed renal cell carcinoma, seven of which were associated with ACKD (category IV). One patient had renal cell carcinoma in the transplanted kidney. Together with 19 patients of the cohort with formerly diagnosed renal cell carcinoma (18 of them associated with ACKD), the prevalence of renal cell carcinoma among all patients was 4.8%; among the patients with ACKD, it was 19.4% (without ACKD 0.5%; P = 0.0001); and among the patients with complex renal cysts (category IIIF to III), it was 54.4%. The patients with ACKD were older (54 ± 13 versus 51 ± 14 yr; P = 0.048), more often male (65 versus 54%; P = 0.03), more often had heart disease (44 versus 29%; P = 0.001), had larger kidneys (6.9 and 6.8 cm versus 6.0 and 5.9 cm; P < 0.001), and had more calcifications (29 versus 15%; P = 0.002). Renal cell carcinoma was bilateral in 26% of cases. Tumor histology was clear cell carcinoma in 58% and papillary carcinoma in 42% of cases; one patient had both. Only one patient had a lung metastasis, and no patient died.

Conclusions: Renal cell carcinoma occurs often after renal transplantation and that especially patients with ACKD should routinely be screened. Because ACKD after renal transplantation seems to be less frequent (23%) than during dialysis treatment (30 to 90%), renal transplantation may inhibit renal cell carcinoma.


Reduced renal function and the development of renal cysts is widely known association (1–4). Acquired cystic kidney disease (ACKD) has been described as cyst formation in a noncystic failing kidney (2). Cysts originate in dilated renal tubules and increase with the duration of renal insufficiency, even after reaching end-stage renal failure (2,3,5,6). Tissue loss that is associated with renal insufficiency may promote hyperplasia of tubular epithelial cells, resulting in cyst formation (2,7), and atypical epithelial proliferation in the cysts may represent the precursor lesion of renal cell carcinoma (8,9). We performed a prospective study in transplant recipients to determine the prevalence of renal cell carcinoma and ACKD and their relationship and the development of complex renal cysts.

Materials and Methods

We studied all patients who received a transplant between 1970 and 1998 and had at least one patient visit to our outpatient clinic between 1997 and 2003. We wrote to the patients and to their nephrologists and asked the patients to have an ultrasound of the native kidneys done by their nephrologist.

Cystic lesions of the kidney were defined according to the Bosniak Renal Cyst Classification System (10,11). That means that cysts that are defined as Bosniak category I and II are benign simple cysts with a hairline thin wall that may contain a few hairline thin septa and fine calcifications but no solid components and no enhancement after contrast media; high-attenuation renal lesions <3 cm may be included. Cysts that are defined as Bosniak category IIF are cysts that may contain multiple hairline thin septa or minimal smooth thickening of their wall or septa or may contain calcifications or intrarenal nonenhancing high-attenuation renal masses ≥3 cm (moderately complex cystic lesions). Cysts that are defined as Bosniak category III show “indeterminate” cystic masses with thickened walls and septa with enhancement after contrast media. Cysts that are defined as Bosniak category IV are clearly malignant cystic masses.

ACKD was defined as more than three cysts in both kidneys. Complex cystic lesions were defined as those with irregularly thickened cyst walls, hyperdense or nonhomogenic cyst content and/or pronounced intrarenal calcifications, and/or positive enhancement after intravenous application of contrast media (Bosniak category IIF to III [10–13]).

Ultrasound was followed by computed tomography (CT) scan or magnetic resonance imaging when a moderately complex cystic lesion of the kidney was found (Bosniak category IIF) or in case of suspicion of renal cell carcinoma (category III or IV; Table 1, Figure 1). Aside from renal cell carcinoma, complex renal cysts, and ACKD, we looked for clinical parameters as possible risk factors or associated conditions for the development of ACKD. We focused on age; gender; time on dialysis treatment; time after renal transplantation; number of transplantations;
Table 1. Recommendation for patient screening of the native kidneys in renal transplant patients according to the Bosniak renal cyst classification (11)

1. All patients should have an ultrasound screening of their native kidneys once a year irrespective of ACKD.
2. Patients with ACKD and cysts according to Bosniak category I and II (benign simple cysts): Ultrasound screening twice a year; CT scan in the case of progressive lesions.
3. Patients with ACKD and cysts according to Bosniak category IIF (moderately complex cystic lesions): Ultrasound screening four times a year; CT or MRI scan once a year; nephrectomy in the case of progressive lesions, even if not reaching category III or IV.
4. Patients with ACKD and cysts according to Bosniak category III ("indeterminate" cystic masses) and IV (clearly malignant cystic masses): Nephrectomy.
5. Patients with ACKD in general: Generous indication for nephrectomy even in the lower categories, if progression occurs, because the original sense of the Bosniak classification (to preserve renal tissue by exact preoperative diagnosis) has lost its importance in patients with end-stage renal failure. This is true especially for cystic lesions of category IIF.

\[ n \text{ACKD, acquired cystic kidney disease; CT, computed tomography; MRI, magnetic resonance imaging.} \]
diagnosed (n = 18) and newly diagnosed (n = 7) patients with ACKD-based renal carcinoma taken together, 25 (19.4%) of 129 patients with ACKD and 25 (54.4%) of 46 with complex cysts had renal cell carcinoma. That means that renal cell carcinoma was significantly more frequent in patients with ACKD than in those without (19.4 versus 0.46%; P = 0.0001).

In 19 carcinomas of 15 patients (58%), the tumor histology was a clear cell carcinoma, and in 14 carcinomas of 12 patients (42%), the tumor histology was a papillary carcinoma (one patient with clear cell plus papillary carcinoma; Figure 2). The tumors often were multifocal or even multiple. In seven (26%) of 27 patients, a bilateral tumor was found (four cases with clear cell and four cases with papillary carcinoma; one patient had a papillary carcinoma of the right side and a clear cell plus a papillary carcinoma of the left side).

The tumor classification was pT1 in 22 cases of 17 patients (11 with clear cell and 11 with papillary carcinoma), pT2 in seven cases of seven patients (four with clear cell and three with papillary carcinoma), and pT3 in five cases of four patients (four with clear cell and one with papillary carcinoma). The tumor was graded G1 in six cases of five patients (five with clear cell and one with papillary carcinoma), G2 in 28 cases of 24 patients (14 with clear cell and 14 with papillary carcinoma), and there was no case with G3. There was no lymph node involvement in any of the patients. One patient with clear cell carcinoma had a lung metastasis, which was successfully treated by operative resection. The tumor of the transplant was classified pT1, N0, M0, and G1 to 2. Bilateral nephrectomy because of suspected tumor was done in 14 of 27 patients; however, the tumor was bilaterally confirmed in only seven cases. The tumor of the renal transplant was successfully treated by pole resection. Unilateral nephrectomy of a complex cystic lesion and suspected tumor without confirmation was done in five cases.

The comparison of the patients with ACKD (n = 129) including those with complex cysts (n = 46) and ACKD-associated renal cell carcinoma (n = 25) with the others without ACKD (n = 432) showed that they were significantly older and more often male, they had significantly more often accompanying cardiac diseases and less often diabetes, and their kidneys were larger and more often had calcifications (Table 2). The comparison of the patients with complex renal cysts (Bosniak category IIF to IV; n = 46) including those with ACKD-associated renal cell carcinoma (n = 25) with those without ACKD (n = 432) showed that they tended to be older (NS), they were significantly more often male, and had significantly more accompanying cardiac diseases and renal calcifications (Table 2). Basic immunosuppression in patients with complex cysts without confirmed malignancy (Bosniak category IIF and III; n = 21) compared with those with confirmed malignancy (Bosniak category IV; n = 25) was not significantly different: Use of prednisolone in 21 of 21 versus 22 of 25 patients (100 versus 88%; NS); use of cyclosporine in 18 of 21 versus 21 of 25 patients (86 versus 84%; NS); use of tacrolimus in two of 21 versus two of 25 patients (10 versus 8%; NS); use of mycophenolate mofetil in six of 21 versus eight of 25 patients (29 versus 32%; NS); use of azathioprine in five of 21 versus five of 25 patients (21 versus 20%; NS); and use of triple therapy in nine of 21 versus nine of 25 patients (43 versus 36%; NS).

The comparison of the patients with confirmed ACKD-associated renal cell carcinoma (Bosniak category IV; n = 25) with those without ACKD (n = 432) showed again that these patients tended to be older and more often male; however, because of the small number of patients, the differences were not statistically significant (Table 2). They had significantly more

Figure 1. Complex cystic lesion of the left shrunken kidney. (A) Computed tomography: Thickened wall with irregular contour and hyperdense cyst content. (B) The same cyst after nephrectomy. (C) The opened cyst reveals renal cell carcinoma.
accompanying cardiac diseases (Table 2). The time after transplantation was significantly shorter in carcinoma patients with ACKD than in the others as was the time since the beginning of ESRD (dialysis and transplantation time together; Table 2).

Discussion

This study shows that the prevalence of patients with renal cell carcinoma in native kidneys after renal transplantation is 5% (previously and newly diagnosed cases together). Furthermore, in patients with ACKD, the prevalence is 19%, and in patients with complex cysts, it is 54%. The simple suggestion from these data to patients and their nephrologists is to perform an additional ultrasound of the native kidneys, an organ check that should be part of the regular posttransplantation patient care at least once a year. Such an examination was followed by the new diagnosis of eight renal cell carcinomas (1.4% of the investigated patients) and the suspicion of three others, which could not be confirmed after nephrectomy. In addition, one renal cell carcinoma of the transplant was found. Because 25 of 27 previously and newly diagnosed renal cell carcinomas were associated with ACKD, this lesion seems to be the basal pre-condition. The prevalence of renal cell carcinoma in ESRD reported in the literature is 0.1 to 7%, with a mean value of 3.2 ± 2.4% (n = 116,906) (5,14–22).

Noteworthy is that this prospective investigation shows a distinctly higher prevalence of renal cell carcinoma (5%) with-
out mortality, compared with a retrospective and historical analysis of all patients from this department who received a transplant between 1968 and 1995. The prevalence of renal cell carcinoma in the retrospective evaluation was 0.5%, and the mortality was 33% (19). This comparison shows that the awareness of the development of renal cell carcinoma of the native kidneys has increased since then and that the tumors are detected at an earlier stage nowadays and therefore have a better prognosis. Nonetheless, the posttransplantation prophylactic patient care in this direction is still not adequate, because in a cross-sectional sonographic check that was done by nephrologists (mostly nonspecialized in ultrasound), additional carcinomas were found in 1.5% of the patients. One cause for the frequent diagnosis of renal cell carcinoma in our investigation may be related to the fact that the willingness to perform a CT scan in suspicious ultrasound cases was pronounced during the study.

It would be interesting to know whether these 12 patients with newly suspected renal cell carcinomas (nine confirmed and three not confirmed by nephrectomy) had not had their yearly ultrasound check for more than 1 yr; however, a realistic answer from their nephrologists cannot be expected. Therefore, the question remains how often and which patients should be checked. One report in the literature showed in a follow-up study of moderately complex cystic lesions of the kidney (Bosniak category IIIf) that two (5%) of 42 patients had developed renal cell carcinoma after 2 to 18 yr (median 5 yr) (23). These were patients without renal insufficiency. That means that in ACKD, we have to suggest a much higher rate of carcinoma development, a theory that can be derived from the high prevalence of renal cell carcinoma in ACKD (19.4%) and from the often observed bilateral carcinoma in ACKD (26% of carcinomas). Table 1 gives a proposal, according to our experience, of how to handle the routine ultrasound and/or CT or magnetic resonance imaging screening in renal transplant patients. The crucial question is whether cystic lesions of the Bosniak category IIIf should be screened or, considering their high rate of malignant changes (54% in our study), they should be treated by early nephrectomy (Table 1).

All carcinomas were clinically inapparent. In all 34 carcinomas of 27 patients (19 preexistent and eight newly diagnosed), we found no lymph node involvement and only one lung metastasis. This benign course may be related to the fact that the tumors were small in these well-observed patients with frequent sonographic checks. The tumor classification was pT1 and pT2 in 85% of carcinomas, and the tumor grading was G1 and G2 in all cases. This finding confirms data that proliferative activity in ACKD-associated renal cell carcinomas is lower than in the sporadic type (24) and that prognosis is better, at least when diagnosed early, than in the sporadic type with 30 to 50% metastasis at diagnosis of the tumor (8).

An evident difference of ACKD associated with sporadic renal cell carcinoma is the much more frequent papillary type in histology, 42% in our series and 10 to 15% in the sporadic type; the clear cell type to the contrary occurred in 58% of cases in our series compared with 70% in the sporadic type (25–27). We did not find any chromophobe renal cell carcinomas in our series. Renal cell carcinoma was frequently bilateral (27% compared with 1% in the sporadic carcinoma) and multifocal, as it is known from the literature (17,27–29). In one patient, we found a bilateral papillary carcinoma together with clear cell carcinoma at one side and renal adenoma at the other (Figure 2).

Renal cell carcinoma was strongly associated with ACKD (19% in patients with ACKD and 0.5% in patients without). This finding means that ACKD seems to be a precondition for the development of renal cell carcinoma. The definition of ACKD is arbitrary. The threshold of cystic changes has not been agreed on and is different in pathologic and radiologic reports (from one to five cysts per kidney, up to 25 to 40% cystic changes of renal tissue [2,5,7,8,15,18,20,21]). The prevalence of ACKD in patients with end-stage renal failure thus varies between 30 and 90% according to the definition of ACKD, the time the patients were on dialysis, and the kind of investigation (autopsy, ultra-
sound, CT, or clinical studies) (2,3,5,12,14,15,20,22,28,30,31). ACKD in our series was associated with older age, male gender, less often diabetes, and more often cardiac diseases (Table 2). An older age and more often male gender is known from the literature (1,12,15,18,20,22,27,29). The reported association of ACKD with nephrosclerosis (2,27) may be the result of the old age and frequent cardiac diseases of these patients.

Surprising, ACKD in our series was not associated with a longer time on dialysis, as has been reported in the literature (1,2,5,12,18,22). Perhaps regression of cysts after renal transplantation may confound this widely known parameter (29,32,33). On the contrary, renal cell carcinoma was even associated with a shorter time of ESRD (Table 2). This state of affairs is probably because suspicious lesions of renal cell carcinoma are operated on as soon as suspected. Considering that renal cell carcinoma was found in 54% of patients with complicated cysts and that the two lesions are not always easy to distinguish, nephrectomy of kidneys with any diagnosed moderately complex cystic lesion (Bosniak category IIF) could be the consequence.

The prevalence of ACKD and the behavior of cyst development after renal transplantation are not well studied. However, the better the renal function, the slower the development. This finding may explain the lower prevalence of ACKD in our series (23%) and that of others after renal transplantation (25%) (18) compared with earlier reports. In dialysis patients, the prevalence of ACKD is said to be 30 to 90% (2,3,5,12,14,15,20,22,28,30,31). Such an incidence would mean that renal transplantation is an indirect prevention of renal cell carcinoma. In this context, we admit that we do not know very much about the influence of immunosuppression on cyst formation. For example, recently, sirolimus was found to have a slowing and even regressing influence on cyst formation. For example, recently, sirolimus was found to have a slowing and even regressing influence on cyst formation. For example, recently, sirolimus was found to have a slowing and even regressing influence on cyst formation.


See the related editorial, “Acquired Cystic Kidney Disease and Renal Cell Cancer after Transplantation: Time to Rethink Screening?” on pages 621–622.