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Prevalence of renal cell carcinoma in patients with ESRD pre-transplantation: A pathologic analysis

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Prevalence of renal cell carcinoma in patients with ESRD pre-transplantation: A pathologic analysis.

Background. Acquired renal cystic disease (ARCD), renal adenoma (AD), and renal cell carcinoma (RCC) are more common in patients with end-stage renal disease (ESRD). However, the prevalence of these conditions in patients undergoing transplantation, and the clinical characteristics associated with their occurrence are unclear.

Methods. At our institution, the majority of patients undergo an ipsilateral native nephrectomy at the time of transplantation, providing a unique opportunity to study the prevalence and pathology of ARCD, AD and RCC in ESRD. We retrospectively reviewed all consecutive nephrectomy pathology reports over a six year period. Demographic and clinical characteristics associated with these lesions were identified.

Results. Two hundred and sixty nephrectomy reports were reviewed: ARCD, AD, RCC and oncocytoma were found in 33%, 14%, 4.2% and 0.6% of cases, respectively. On multivariable analysis, ARCD was positively associated with male sex and longer dialysis duration and negatively associated with peritoneal dialysis. Similarly, AD was positively associated with male sex, longer dialysis duration and greater age. There was a trend for RCC cases to share similar associations although the small total number of cases precluded findings of statistical significance.

Conclusion. By pathologic analysis, renal tumors are more common in the pre-transplant ESRD population than previously reported (using radiologic methods). Our study also identifies risk factors for their occurrence. This may prove useful in designing screening studies for renal tumors in this patient population.

Acquired renal cystic disease (ARCD) is characterized by the development of multiple cysts in the kidneys of patients with end-stage renal disease (ESRD), in the absence of congenital cystic disease [1, 2]. Although microscopic cysts can be identified in the kidney biopsies of some patients with chronic renal impairment [3], cysts are not usually detected radiologically until the development of ESRD. ARCD increases in prevalence and severity with increasing years on dialysis: 20% of patients dialyzed for 1 to 3 years have ARCD, compared with greater than 90% of patients dialyzed for 5 to 10 years [2]. The prevalence of renal cell carcinoma (RCC) also is increased in patients with ESRD on dialysis [4] and in patients after renal transplantation [5]. By ultrasound, RCC was identified in the native kidneys of 3.8% and 3.9% of ESRD patients pre- and post-transplantation, respectively [4, 5], which represents a 100-fold increase in prevalence compared to the general population.

Most studies examining the prevalence of ARCD and RCC in the ESRD population are based on radiological detection. However, radiological techniques may underestimate the true prevalence of ARCD and RCC due to limitations in resolution. At our institution, ureteropyelostomy, using the recipient ureter, is the preferred method of urinary tract reconstruction for renal allograft recipients who are free of vesicoureteric reflux or other ureteral abnormalities [6]. Thus, ipsilateral native nephrectomy is performed on the majority of patients undergoing renal transplantation. All nephrectomy specimens are examined macroscopically, microscopically and by immunofluorescence. Using this unique database, we performed a retrospective analysis to determine the prevalence of ARCD, AD and RCC in ESRD patients undergoing renal transplantation. This study identifies clinical risk factors associated with RCC that may provide a framework for selective screening of the pre-transplant population.

METHODS

From January 1994 to January 2000, 349 renal transplants were performed in our institution. In 260 patients a native nephrectomy and uretoropyelostomy were performed; the remaining patients underwent standard

Key words: acquired cystic disease, kidney cancer, transplantation, end-stage renal disease, renal tumors, selective screening population study.

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ureteroneocystostomies. The principle reason for not performing nephrectomy and ureteropyelostomy was a history of vesicoureteric reflux. The medical records of all patients who had had a nephrectomy were examined and the following clinical information was systematically extracted: age, sex, primary renal disease, dialysis modality, and duration. Data on smoking history were not uniformly available. Diagnosis of primary renal disease was based on clinical history, histologic examination of prior biopsy samples or the nephrectomy specimen.

At the time of nephrectomy, specimens were thinly sliced at 0.5 cm intervals and examined macroscopically for cysts and tumors. Routinely, 3 to 5 random sections were examined by hematoxylin and eosin (H&E) and periodic acid-Schiff (PAS) staining for original disease as well as for the presence of acquired renal cystic disease and neoplasia, including benign tumors (adenoma, oncocytoma) and renal cell carcinoma. In addition, sections from gross lesions were examined. Pathologic criteria for the presence of ARCD included scattered macroscopic cystic structures occupying more than 25% of the renal parenchyma or >3 cysts per kidney [7]. The renal tumors were characterized by histologic type, as classified by the Heidelberg classification [8]. The criteria of Grignon and Eble were used for papillary lesions, that is, tumors with a diameter less than 0.5 cm were considered adenomas [9]. All clear cell tumors were considered malignant according to the view of these authors. The renal cell carcinomas were graded according to a four-tier system based on nuclear size, shape and content as proposed by Fuhrman et al [10]. Staging was performed using the TNM system [11]. All cases of RCC were subsequently confirmed at the time of analysis by two authors (SM and RC). The prevalence of ARCD, AD and RCC were determined and correlated with clinical variables by retrospective analysis of the database. Follow-up abdominal imaging after transplantation in cases with RCC also was done.

Statistical analysis

Descriptive and univariable analysis. Categorical predictors were first tabulated to determine whether adequate numbers (for meaningful statistical analyses) existed per category and thus whether to group or leave unchanged. Grouping was then only performed if clinically relevant. In each analysis, the outcome was a binary variable: ARCD/no ARCD and AD/no AD. Categorical predictors were individually compared to the outcomes by Fisher's exact test; continuous variables were compared using the Wilcoxon rank sum test.

Multivariable analysis. Logistic regression was then used for determination of predictors significantly associated with each of the three different outcomes (presence of ARCD, presence of AD, presence of RCC). All predictors were carried forward to the regression model (even if not significant by univariable analysis), as the purpose of the study was to identify all possible clinical or statistically significant predictors. Where more than two categorical variables existed, dummy coding was performed. Variables that became non-significant in the multivariable models were tested for colinearity and confounding.

Results are presented as odds ratios with 95% confidence intervals and with P values. A P value <0.05 was considered statistically significant. SAS (Cary, NC, USA) was used for statistical analysis.

Table 1. Demographic and clinical characteristics of the 260 patients who underwent nephrectomy

Characteristic	*N* (%)
Sex	
Male	161 (61.9)
Race	
White	207 (79.6)
Black	27 (10.4)
Hispanic	15 (5.7)
Asian	12 (4.6)
Dialysis	
Total	209 (80.3)
HD	162 (62.3)
PD	47 (18.1)
Primary disease	
GN	95 (36.5)
DM	54 (20.7)
PKD	33 (12.7)
HTN	18 (6.9)
CP/reflux	14 (5.4)
Dysplasia	8 (3.1)
Others	38 (14.6)
Mean or median	
Age *years*	42.7 (mean) ± 12.7 (SD)
Dialysis duration *years*	1.0 (median); 0–16 (range)

Abbreviations are: HD, hemodialysis; PD, peritoneal dialysis; GN, glomerulonephritis; DM, diabetes mellitus; PKD, polycystic kidney disease; HTN, hypertension; CP, chronic pyelonephritis.

RESULTS

Population characteristics

The demographic and clinical characteristics of the 260 patients who underwent native nephrectomy at transplantation are listed in Table 1. Over 60% were male; the majority were white and almost 2/3 were on dialysis prior to transplantation. Further analysis compared whites to non-whites. Interestingly, the most commonly identified cause of primary renal disease was glomerular in origin and included IgA nephropathy, membranoproliferative glomerulonephritis, membranous glomerulonephritis, focal segmental glomerulosclerosis and crescentic glomerulonephritis.

Acquired renal cystic disease

Of all nephrectomy specimens with ESRD, 33% (85/260) had ARCD (Fig. 1B) characterized by the presence of variable sized cysts scattered in the renal parenchyma

lined by flat or cuboidal epithelium that focally showed reactive nuclear changes and micropapillary projections. The cysts were scattered singly or sometimes in small clusters.

The demographic and clinical characteristics of patients grouped according to the presence or absence of ARCD are listed in Tables 2 and 3. On univariable analysis (Table 2), patients with ARCD were older, more likely to be male, to have undergone hemodialysis and to have a primary renal diagnosis of glomerulonephritis compared to patients without ARCD. No difference in race was noted between the groups. The mean duration of dialysis was significantly longer in patients with ARCD. No difference between the two groups was seen with regard to "exposure" to peritoneal dialysis. The adjusted (multivariable) analysis (Table 3) showed that only male sex and dialysis duration were significantly associated with the presence of ARCD. Interestingly, peritoneal dialysis was inversely associated with ARCD on the adjusted analysis; the lack of significance in univariable analysis mainly reflected negative confounding by dialysis duration.

Renal adenomas

Renal adenomas were identified in 14% (35/260) of the end-stage kidneys. AD were typically 0.2 to 0.4 cm in diameter in our series and showed either a papillary, tubular, or tubulopapillary pattern, without clear cell change or nuclear abnormalities, consistent with papillary renal adenomas (Fig. 1C).

The demographic and clinical characteristics of patients grouped according to the presence or absence of AD are listed in Table 4 (univariable analysis) and Table 5 (multivariable analysis). On univariable analysis, patients with AD shared similar characteristics to those with ARCD including greater age, a higher likelihood of male sex, and longer dialysis duration. Interestingly, the presence of AD was again correlated with the primary renal disease. Patients with AD were significantly more likely to have a glomerulonephritis as the primary renal disease. In contrast, diabetes inversely correlated with the presence of AD. Indeed, diabetes was the underlying cause of ESRD in only one patient (2.9%) with an AD in contrast to a prevalence of 23.6% in patients without AD. On multivariable analysis (Table 5), age, male sex and dialysis duration were associated with AD, and again diabetes was inversely associated. Glomerulonephritis was no longer significantly associated with the presence of AD on multivariable analysis after adjusting for the confounding variables diabetes and the male sex. Patients with AD were more likely to have underlying ARCD (odds ratio 3.8 (1.8 to 7.9) ($P < 0.001$).

Renal cell carcinoma

Twelve cases of renal cell carcinoma were identified from the database. One case was reclassified as an oncocytoma. The clinical and pathological features of the 11 cases of RCC are outlined in Table 6. RCC was detected in 4.2% (11/260) of the nephrectomy specimens. Of these, 55% (6/11) had conventional, clear cell, renal carcinoma (Fig. 1E), with cystic change in three cases. Four of the remaining cases and one case that also had coexisting clear cell carcinoma, were papillary renal carcinomas (45%; Fig. 1F); three basophilic type (type 1) and two eosinophilic type (type 2). The remaining case was a chromophobe renal carcinoma (9%) with positive staining for colloidal iron (Fig. 1 G, H). All the renal cell carcinomas in our series were T1N0M0 lesions (stage I), limited to the kidney.

In the 11 cases of RCC, 91% (10/11) had underlying ARCD and 73% (8/11) had coexisting papillary AD. Indeed, RCC was highly associated with both ARCD (OR 6.0, 1.5 to 23.1; $P < 0.007$) and AD (OR 38.6, 7.9 to 188.3; $P < 0.001$). In 36% (4/11) of cases, subsequent radiological investigation revealed the presence of a tumor (confirmed in all cases by subsequent histology) in the contralateral kidney. The majority of bilateral tumors exhibited papillary morphology. The clinical characteristics of patients grouped according to the presence or absence of RCC are listed in Table 7 (univariable analysis) and Table 8 (multivariable analysis). On multivariable analysis only age reached significance; there was only a trend towards significance with male sex and dialysis duration probably because group numbers were small.

Patients were followed for a mean of 31.3 ± 22.5 months after transplantation. During this period, two more cases of RCC were diagnosed in the contralateral native kidney, found incidentally on radiological examination. Neither patient had previously been diagnosed with RCC. No cases of metastatic renal cell carcinoma occurred.

DISCUSSION

Dunhill, Millard and Oliver first described the association of ARCD and RCC with hemodialysis [12]. In his autopsy study of 40 patients, 46% had ARCD and 15% had a renal tumor. Miller et al subsequently reported a larger autopsy series of 155 hemodialysis patients in which ARCD was noted in 58%, renal adenoma in 16%, and RCC in 2% of patients [13]. Further studies have shed light on the prevalence, risk factors and natural history of both ARCD and RCC in ESRD patients (both before and after renal transplantation) [4, 5, 14, 15]. Most of these studies have utilized ultrasound screening that may have underestimated the true prevalence of RCC due to limitations in resolution. Since we perform ipsilateral nephrectomy on most patients who undergo renal transplantation, we have been able to construct a unique database consisting of detailed histology on native renal tissue from pre-transplant patients. Using this database, our current study reports the largest pathologic analysis,

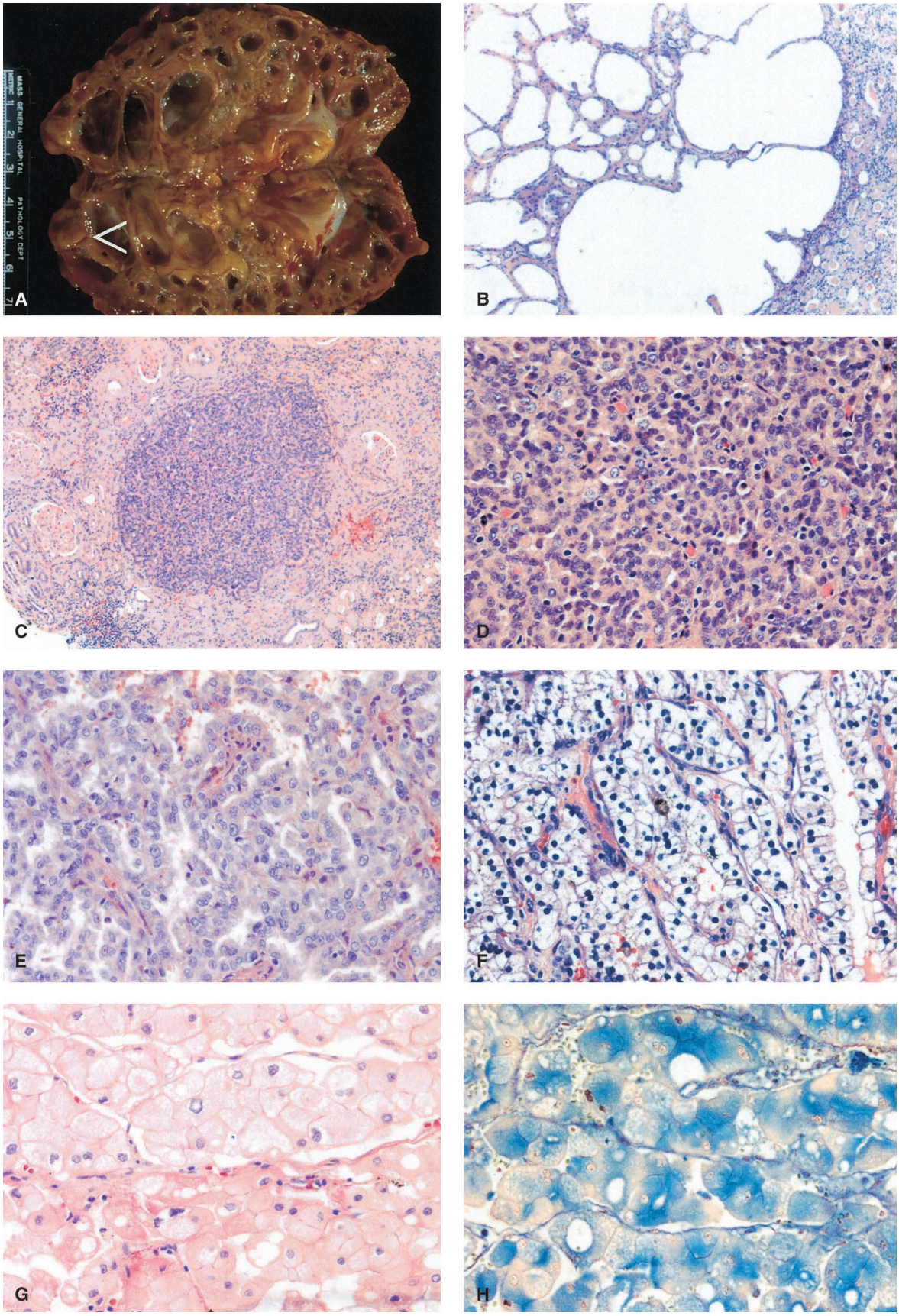
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Table 2. Univariable analysis of demographic and clinical characteristics of patients with ARCD ($N = 85$) and without ARCD ($N = 175$)

Characteristic	ARCD	No ARCD	Odds ratio (CI)	*P* value (Fisher's)
	N (%)			
Male	66 (77.7)	95(54.3)	2.9 (1.6–5.3)	<0.001
White	69 (81.2)	138 (78.9)	1.2 (0.6–2.2)	0.869
Dialysis				
All	74 (87.1)	135 (77.1)	2.0 (0.97–4.1)	0.068
HD	62 (72.9)	100 (57.1)	2.0 (1.2–3.6)	0.014
PD	12 (14.1)	35 (20.0)	0.7 (0.3–1.3)	0.303
Primary Disease				
GN	39 (45.9)	56 (32.0)	1.8 (1.1–3.1)	0.039
DM	13 (15.3)	41 (23.4)	0.6 (0.3–1.2)	0.145

Characteristic	ARCD	No ARCD	*P* value (Wilcoxon RS)
	Mean (SD)		
Age *years*	45.8 (11.3)	41.2 (13.1)	0.0062
Dialysis duration *years*			
Mean (SD)	3.1 (2.82)	1.28 (1.43)	0.0001
Median	2	1	

to our knowledge, of the prevalence of ARCD, AD and RCC in patients with ESRD awaiting renal transplantation. The strengths of this study are the large number of patients (which permitted multivariable analysis) and the use of pathological data to determine precisely the presence of ARCD, AD and RCC. Furthermore, as biopsy of native kidneys is not always performed in patients with chronic renal failure, pathological analysis allowed better determination of primary renal disease in some cases. Although this is a retrospective study, sampling bias has been limited because all consecutive cases were examined within the time period chosen, and because pathologic analysis and data collection were performed in a systematic manner. Furthermore, all cases of RCC were re-examined by an independent pathologist.

The prevalence of ARCD reported here is similar to that reported by Gulanikar et al, who screened a similar population of patients by ultrasound [4]. Consistent with most previous reports [2], we found a strong association between the prevalence of ARCD and dialysis duration, even after adjustment for other variables. When dialysis modality was examined by multivariable analysis, we found that patients on peritoneal dialysis were significantly less likely to have ARCD. This finding contrasts with those of other groups [16–18]; however, in these studies statistical analysis did not adjust for confounding variables. In our population, peritoneal dialysis was negatively confounded by a longer duration of dialysis. Dialysis duration was shorter in the HD group compared to the PD group probably because most patients who are destined for living related transplantation and therefore a short course of dialysis are put on HD rather than PD in our institution.

We also found that ARCD was more common in males

Table 3. Multivariable analysis of demographic and clinical characteristics associated with ARCD

Characteristic	Odds ratio (CI)	*P* value
Age	1.0 (1.0–1.1)[a]	0.072
Male	3.1 (1.5–6.3)	0.002
White	1.3 (0.6–2.8)	0.48
HD	0.5 (0.2–1.3)	0.147
PD	0.3 (0.1–0.9)	0.04
Dialysis duration	1.9 (1.5–2.5)[b]	<0.001
GN	1.7 (0.8–3.3)	0.161
DM	0.6 (0.3–1.5)	0.281

[a] Per year of age
[b] Per year on dialysis

Fig. 1. End-stage renal disease. (*A*) Macroscopic picture of bivalved kidney with acquired renal cystic disease (ARCD) and renal cell carcinoma (RCC) (<). (*B*) ARCD in a patient on chronic hemodialysis. The cysts are lined by flattened or cuboidal epithelium that form micropapillary projections (H&E stain; original magnification; A, ×200; B, ×200). (*C*) Papillary renal adenoma showing a microscopic nodular cortical lesion in an end stage kidney. (*D*) Higher power of the papillary adenoma, densely packed tubulopapillary architecture lined by small cuboidal cells with uniform nuclei that lack cytologic atypia (H&E, original magnification; C ×100; D, ×400). Renal cell carcinoma in end-stage renal disease cases: (*E*) Papillary renal carcinoma, tumor cells containing vesicular nuclei with prominent nucleoli arranged in papillary structures with fibrovascular stalks. (*F*) Conventional, clear cell renal carcinoma, sheets of tumor cells with abundant clear cytoplasm and central nuclei. Some tubular differentiation and intervening vascular stroma are present. (*G*) Chromophobe renal cell carcinoma, large tumor cells with abundant pale pink cytoplasm with sharply defined borders, large pleomorphic nuclei and perinuclear clearing. (*H*) Blue cytoplasmic staining for the presence of colloidal iron, characteristic of chromophobe renal cell carcinoma (same tumor shown in G). (H&E stain, original magnification; E, ×400; F, ×400; G, ×400. Hale's colloidal iron stain, original magnification; H, ×400).

Table 4. Univariable analysis of demographic and clinical characteristics of patients with adenoma ($N = 35$) and without adenoma ($N = 225$)

Characteristic	Adenoma	No adenoma	Odds ratio (CI)	*P* value (Fisher's)
	N (%)			
Male	30 (85.7)	131 (58.2)	4.3 (1.6–11.5)	0.001
White	32 (91.4)	175 (77.8)	3.1 (0.9–10.3)	0.073
Dialysis				
All	30 (85.7)	179 (79.6)	1.5 (0.6–4.2)	0.496
HD	25 (71.4)	137 (60.9)	1.6 (0.7–3.5)	0.265
PD	5 (14.2)	42 (18.7)	0.7 (0.3–2.0)	0.64
Primary disease				
GN	19 (54.3)	76 (33.8)	2.3 (1.1–4.8)	0.024
DM	1 (2.9)	53 (23.6)	0.1 (0.01–0.7)	0.003
Characteristic	Adenoma	No adenoma	*P* value (Wilcoxon RS)	
	Mean (SD)			
Age *years*	48.8 (10.3)	41.7 (12.8)	0.002	
Dialysis duration *years*				
Mean (SD)	2.99 (2.23)	1.71 (2.11)	<0.001	
Median	3	1		

Table 5. Multivariable analysis of demographic and clinical characteristics associated with adenoma

Characteristic	Odds ratio (CI)	*P* value
Age	1.04 (1.0–1.1)[a]	0.023
Male	6.8 (2.0–23.3)	0.002
White	3.3 (0.9–12.1)	0.067
HD	1.8 (0.4–7.5)	0.398
PD	1.3 (0.3–6.8)	0.729
Dialysis duration	1.2 (1.0–1.4)[b]	0.031
GN	1.6 (0.7–3.8)	0.281
DM	0.1 (0.1–0.8)	0.034

[a] Per year of age
[b] Per year on dialysis

[18]. Indeed, males tend to develop more extensive cystic changes, in addition to having a greater preponderance for the disease [18, 19]. Previous reports have found an increased prevalence rate of ARCD in blacks [2]. No significant racial predilection was found in our study although numbers of non-whites were small. Finally, several studies have reported an association between ARCD and primary glomerulonephritis [20, 21]. Although we found ARCD and glomerulonephritis to be associated on univariable analysis, the association was not significant on multivariable analysis. Thus, our series provides further confirmation of the clinical factors associated with ARCD identified by previous (radiology based) studies but, importantly, does so by using "gold standard" pathology criteria and by using adjustment for confounding factors.

Our study is the first to our knowledge to identify demographic and clinical characteristics associated with the presence of AD in patients with ESRD. The overall prevalence of AD was 14%. Age, male sex and dialysis duration strongly correlated with the presence of AD, as did the presence of glomerulonephritis by univariable analysis only. Here we found that diabetes mellitus was negatively associated with AD on the adjusted analysis, an observation not previously reported. Others have found that diabetics are less likely to have ARCD [22] and have suggested that this is because diabetics have a shorter survival on dialysis. This would not explain our findings since we adjusted for dialysis duration. Two possible explanations are that (*i*) this was a chance finding or (*ii*) the diabetics in our study had a shorter total period of "exposure" to chronic renal failure + dialysis since, similar to other centers, diabetics in our units are often started on dialysis at a higher GFR than non-diabetics.

Eleven cases of RCC were identified, giving a prevalence rate of 4.2%. This rate is over 100-fold higher than that reported by Tosaka et al for a general unselected population on ultrasound screening [23]. Special consideration must be taken when extrapolating the prevalence found in our study to that of the general ESRD population. Firstly, we are sampling only one of two native kidneys so the true prevalence rate could actually double, that is, to 8.4%. However, 4 of 11 (36%) of our patients had bilateral renal cell carcinomas and Gulanikar et al (using radiological techniques) [4] found bilateral lesions in 2 of 8 (25%) patients. Thus, the true prevalence of renal cell carcinoma in our sample is between 4.2% and 8.4%, approximately 30% less than the maximum prevalence. Secondly, our sample population is not completely representative of the entire ESRD population due to the exclusion of non-transplant ESRD patients and some groups of pre-transplant patients that did not undergo a native nephrectomy (for example, most patients with reflux nephropathy). Our prevalence rate is greater than those reported by studies using ultrasound screening (3.8% and 3.9% of ESRD patients pre- and post-transplantation, respectively), probably because we were able

Table 6. Clinical and pathological characteristics of patients with RCC ($N = 11$)

Age	Sex	Race	Primary disease	Dialysis	Dialysis duration	ARCD	Adenoma	Multifocal CA	Furhman grade	Size	Type
62	M	W	ESRD	PD	3	Y	Y	Y	3	3.5	Papillary[a]
53	M	H	Nephrolithiasis	NO	0	Y	Y	N	3	0.5	Chromophobe
54	M	W	Chronic GN	HD	10	Y	Y	Y	3	1.2	Clear cell
51	M	W	DM	HD	4.5	Y	N	N	2	1	Papillary[b]
48	M	W	ESRD	HD	4	Y	Y	Y	3	0.7	Papillary[b]
53	M	W	MPGN	HD	3	Y	Y	Y	1	0.2[c] & 0.5[d]	Clear cell and papillary[a]
42	M	H	Chronic GN	PD	1	Y	N	N	1	0.4	Clear cell
54	M	W	MGN	HD	3	N	Y	N	2	0.8	Papillary[b]
46	M	W	IgA	NO	0	Y	Y	N	1	1.2	Clear cell
69	F	B	MGN	HD	4	Y	N	N	1	1	Clear cell
51	M	W	IgA	HD	4.5	Y	Y	N	2	0.5	Clear cell

Abbreviations are: DM, diabetes mellitus; FSGS, primary focal segmental glomerulosclerosis; MGN, membranous glomerulonephritis; ESRD, end-stage renal disease; MPGN, membranoproliferative glomerulonephritis; IgA, IgA nephropathy.

[a] Eosinophilic type
[b] Basophilic type
[c] 0.2 cm clear cell carcinoma
[d] 0.5 cm papillary carcinoma

Table 7. Univariable analysis of demographic and clinical characteristics of patients with RCC ($N = 11$) and without RCC ($N = 249$)

Characteristic	RCC	No RCC	Odds ratio (CI)	P value (Fisher's)
	N (%)			
Male	10 (90.9)	151 (60.6)	6.5 (0.8–51.5)	0.056
White	9 (81.8)	198 (79.8)	1.1 (0.2–5.4)	1.0
Dialysis				
All	9 (81.8)	203 (82.2)	0.8 (0.2–4.7)	1.0
HD	7 (63.6)	155 (63.5)	1.0 (0.3–4.7)	1.0
PD	2 (18.2)	45 (18.4)	0.9 (0.2–4.7)	1.0
Primary disease				
GN	7 (63.6)	88 (35.3)	3.2 (0.9–11.2)	0.110
DM	1 (9.1)	53 (21.3)	0.37 (0.04–3.0)	0.470

Characteristic	RCC	No RCC	P value (Wilcoxon RS)
	Mean (SD)		
Age *years*	52.6 (6.4)	42.3 (11.7)	0.004
Dialysis duration *years*	3.0 (2.8)	1.8 (2.1)	0.134

Table 8. Multivariate analysis of demographic and clinical characteristics associated with RCC

Characteristic	Odds ratio (CI)	P value
Age	1.1 (1.0–1.2)[a]	0.013
Male	10.8 (0.8–149.0)	0.077
White	0.8 (0.2–4.4)	0.832
HD	0.4 (0.1–2.8)	0.375
PD	0.6 (0.07–5.9)	0.688
Dialysis duration	1.3 (0.99–1.60)[b]	0.078
GN	3.0 (0.7–13.6)	0.143
DM	0.8 (0.1–9.1)	0.88

[a] Per year of age
[b] Per year on dialysis

to detect very small tumors. Indeed, three tumors were less than or equal to 0.5 cm, which is below the minimum size detectable by ultrasound scanning.

The majority of RCC occurred in the setting of ARCD (91%) and AD (73%). Although the presence of ARCD might have biased the reviewing pathologist to look more closely for RCC in a given histological specimen, we believe the contribution of such bias is unlikely to have fully explained such a strong association. Furthermore, patients with ARCD, AD and RCC all shared common clinical characteristics. Although the number of patients with RCC is too small to provide adequate statistical power for analysis, we found that RCC patients had the higher mean age of any group and all but one tumor occurred in males. There was also a trend towards longer duration of dialysis in those with RCC compared to those without. Of note, only one patient with RCC had diabetes compared to seven with a primary renal diagnosis of glomerulonephritis. These findings support the notion that ARCD, AD and RCC share common pathophysiologic factors. Indeed, histopathologic studies of ARCD have shown cellular changes suggesting that many of the RCC may have developed from papillary cystic hyperplasia, in a manner analogous to the adenoma-carcinoma sequence of the colon [24]. The pathogenic mechanisms

of cyst formation and RCC have not been elucidated. There is an enhanced expression of growth factors (platelet-derived growth factor and epidermal growth factor) and mutagens in end-stage kidneys although the mechanism promoting their expression is unknown [25, 26]. The uremic milieu seems to be an important factor; transplantation and restoration of normal renal function are associated with regression of ARCD [27]. The strong association with male sex suggests an important role for endogenous substances such as androgens. Failure of immune surveillance due to immunosuppressive effects of uremia may account for tumor development and the frequent multifocal nature of RCC in ESRD.

Increasing evidence suggests that the genetic mechanisms underlying development of RCC in the setting of ESRD are different from those underlying sporadic RCC in the general population. First, in ESRD there is an overrepresentation of papillary RCC: whereas papillary RCC usually comprises only 10 to 15% of sporadic cases, in this study and others, papillary RCC represented over 30% of tumors [28]. Second, sporadic papillary tumors but not ESRD papillary tumor usually show allelic duplications of chromosomes 7 and 17 [29]. Typically RCC in the setting of ESRD is not associated with the p53 gene mutation [14].

Given the increased prevalence of RCC in patients with ESRD, how aggressively should the dialysis and transplant population be screened for RCC? Current practice is not to screen dialysis patients based on the apparent indolent nature of incidentally detected RCCs in patients with ESRD and poor long-term survival in this patient population. Endreny, Cronan and Chazan commented that despite a high prevalence of ARCD in their dialysis population they had no cases of metastatic RCC in 800 dialysis patients [30]. In a series of 831,804 dialysis patients followed up for an average of 2.5 years, 2053 (0.25%) patients were diagnosed with renal cancer, representing a 3.6-fold increased risk over the general population [31]. No information was given on tumor staging. In a recent report, Takebayashi et al commented on the growth rate and behavior of RCC in dialysis patients as determined by serial helical computed tomography (CT) scanning [32]. Their main finding was the high variability in growth rate between tumors.

Because of the hazards of chronic immunosuppression, transplant recipients represent a population potentially at greater risk of metastatic disease. Immunosuppressive agents may accelerate tumor growth, both indirectly by suppressing tumor surveillance and, in the case of cyclosporine A, directly via inducing transforming growth factor-beta (TGF-β) expression. Despite these concerns, the incidence of metastatic RCC does not appear to be high in the transplant population. Some argue that this is due to regression of ARCD post-transplantation [1]; however, the prevalence of non-metastatic RCC remains high [5]. Perhaps renal tumors developing in the setting of ESRD represent a unique subtype of RCC with inherent low metastatic potential. Kliem et al reported outcome in 2372 renal transplant patients [33]; 12 cases of RCC were identified, of whom 4 died as a direct consequence of the tumor despite nephrectomy. Ondrus et al reported 2 cases of metastatic RCC in 620 renal transplant patients [34]. In our series, no cases of metastatic RCC developed in 349 patients transplanted during a follow up period of 31.3 ± 22.5 months. This may be an underestimate because first, the majority of our patient population already had one native nephrectomy, and second, a systematic search for metastatic RCC was not conducted in our study population.

In summary, our results suggest that renal tumors are common in the pre-transplant ESRD population. Undoubtedly, some of these cases may progress to more invasive RCC. Current guidelines set by the American Society of Transplant Physicians suggested that routine screening of transplant patients is not warranted. We suggest that a screening program aimed at those at highest risk of RCC merit further investigation and prospective study. Our analysis suggests an effective method of designing such a study because risk factors associated with the development of RCC in the ESRD population are identified.

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