Renal Cell Carcinoma and End Stage Renal Disease

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Purpose: Patients with ESRD secondary to acquired renal cystic disease have been reported to have a higher incidence of RCC than the general population. We examined the clinical and pathological significance of incidental renal masses in patients with ESRD.

Materials and Methods: From January 1994 to July 2000, 852 consecutive patients with ESRD who were being considered for renal transplantation at University of Mississippi Medical Center were evaluated with renal ultrasound as part of assessment for possible kidney transplantation. Those patients with ultrasound suspicious for a malignant renal lesion were further evaluated with CT of the abdomen with and without intravenous contrast medium. Any patient with CT findings suspicious for RCC was recommended to undergo radical nephrectomy before kidney transplantation.

Results: A total of 19 patients had CT criteria for a possible malignant renal lesion. Seven patients had Bosniak class 3 renal cysts and 12 patients had solid, enhancing renal masses. Of the patients 17 underwent radical nephrectomy. On pathological examination 14 patients had RCC with a 1.64% prevalence in the population screened. Mean Fuhrman nuclear grade in our patients was 2.45.

Conclusions: RCC in patients with ESRD are of clinical significance, considering the size, grade, histology and pathological stage of these tumors. The higher prevalence of clinically significant RCC in patients with ESRD as well as the risk of cancer progression while patients are on immunosuppressive medications justifies screening for RCC in patients with ESRD who are awaiting renal transplantation.

Key Words: kidney; carcinoma, renal cell; cysts; kidney failure, chronic; kidney transplantation

Dunnill et al first described the development of ARCD in patients with ESRD.[1] Diagnostic criteria for the diagnosis of ARCD are macroscopic cystic structures compromising at least 25% of the renal parenchyma or greater than 3 cysts per kidney.[2] Of patients on dialysis for less than 3 years 10% to 20% have ARCD, 40% to 60% on dialysis for 3 years have ARCD and more than 90% have ARCD after 5 years on dialysis.[3] ARCD has been considered a factor predisposing to RCC.[1]

There are numerous conflicting studies regarding the incidence and clinical significance of RCC in the ESRD population. In their studies Chandhoke[4] and Tosaka[5] et al did not observe an increase in RCC in patients with ESRD compared to the general population (0.04%). Gehrig et al noted a 4% incidence in RCC in patients with ARCD.[6] Terasawa et al reported a 2.6% incidence of RCC in their 1,603 patients on hemodialysis.[7] We prospectively followed patients with ESRD to determine the incidence of RCC and the clinical significance of RCC.

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MATERIALS AND METHODS

From January 1994 to July 2000, 852 consecutive patients with ESRD who were candidates for renal transplantation at University of Mississippi Medical Center were evaluated with renal US as part of assessment for possible renal transplantation. Patients who had an US finding suspicious for renal malignancy were further evaluated with CT of the abdomen with and without intravenous contrast material with thin cuts through the kidneys. Any patient with CT suspicious for RCC was recommended to undergo radical nephrectomy before renal transplantation. Patients were excluded from future renal transplantation if they did not undergo further investigation of and treatment for the suspicious renal mass. Patients with normal renal US were not routinely re-screened at University of Mississippi Medical Center.

RESULTS

A total of 19 patients had CT criteria for a possible malignant renal lesion. Seven patients had Bosniak class 3 renal cysts and 12 had solid, contrast enhancing masses on CT. Radical nephrectomy was recommended to all 19 patients but 2 refused surgery. Seven patients underwent left radical nephrectomy, 5 underwent right radical nephrectomy and 5 underwent bilateral nephrectomy. Most radical nephrectomies were performed via an 11th rib supracostal approach.

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Pathological results			
Size (cm)	No. Papillary	No. Clear Cell	Stage (No. pts)
Less than 2.5	2	2	T1 (4)
2.5–4.0	5	1	T1 (6)
4.0–7.0	1	2	T1 (2), T3a N0 (1)
7.0–10.0	0	1	T3aN1 (1)

Four patients underwent hand assisted laparoscopic nephrectomy and a chevron incision was used in 5 with bilateral renal tumors. The adrenal gland was removed in patients with upper pole renal tumors and when the adrenal gland appeared suspicious. Of the 17 patients who underwent surgery 13 were male and 4 were female. Of the patients 14 were black and 3 were white. Mean age of the patients undergoing nephrectomy was 48 years (median 45). This cohort of patients had a mean 9-year history on dialysis (median 8). Five patients had ADPCKD and 12 had ARCD.

On pathological examination 14 patients had RCC with a prevalence of 1.64% in screened patients with ESRD. Of the patients 11 (79%) with RCC had ARCD. The remaining 3 patients with RCC had ADPCKD. Bilateral RCC was noted in 2 patients with ARCD and in 1 with ADPCKD. Seven patients had 1 tumor, 4 had 2 tumors and 3 had 3 tumors. Mean Fuhrman nuclear grade of the tumors was 2.45. Eight patients (57%) had papillary RCC and 6 (43%) had clear cell RCC.

Ten patients with ESRD presented with tumors less than 4 cm. None of these 10 patients had evidence of metastatic disease. Four patients (29%) presented with tumors greater than 4 cm, of whom 1 had adrenal involvement with nodal metastasis and 1 had adrenal involvement without nodal disease (table 1).

DISCUSSION

There are approximately 150,000 patients on dialysis in the United States. In more than 90% of these patients ARCD develops if they are placed on dialysis for greater than 5 years.[3] ARCD is associated with the duration of dialysis.[8] ARCD has a similar incidence in patients treated with hemodialysis and peritoneal dialysis.[9] To our knowledge the etiology of ARCD has not been proved. Leading theories about the development of ARCD include saccular and fusiform expansion of obstructed distal tubules and collecting ducts from oxalate crystals, interstitial fibrosis and tubular epithelial hyperplasia.[10] Papillary ischemia may result in papillary necrosis and lead to the obstruction of tubules.[11] A cystogenic nephrotoxin that is not cleared by dialysis may result in ARCD.[12]

There has been much debate whether ARCD and ESRD are associated with RCC. Chandhoke[4] and Tosaka[5] et al did not detect an increased prevalence of RCC in the ESRD population compared to that in the general population. However, Miller[13] and Terasawa[7] et al observed a significantly increased prevalence of RCC in patients with ESRD.

Of our 852 patients with ESRD 14 had RCC for a 1.64% prevalence of RCC in patients with ESRD. This is significantly greater than the incidence of RCC in the general patient population (0.04%). Half of the tumors in our ESRD patient population were multifocal. Of RCCs in our ESRD patient population 57% were papillary variants compared to a 10% incidence of papillary RCC in the general population. Clear cell RCC was present in only 43% of our patients with ESRD compared to 80% with clear cell RCC in the general population. Ishikawa and Kovacs also noted an increased proportion of papillary RCC in patients with ESRD.[14] In addition, Storkel et al observed an increased incidence of papillary RCC in patients with ARCD.[15]

Papillary RCC differs from conventional RCC in regard to genetic alterations. Some groups have noted that patients with papillary RCC tend to have a better prognosis than patients with clear cell RCC.[16] However, to our knowledge stage for stage no significant difference in outcome between clear cell and papillary RCC has ever been demonstrated.

One patient in our series presented with metastatic disease. In the series of Pope et al only 1 patient on dialysis presented with metastatic RCC.[2] A third of the patients in the general population have metastasis when they present with RCC. Hoshida et al reported that renal cell tumors in patients on dialysis were approximately half the size of sporadic RCCs.[17] Since most renal cell tumors are small, confined to the renal capsule and without evidence of metastasis in patients on chronic hemodialysis, questions regarding the clinical significance of RCC in the long-term maintenance dialysis population have been raised. Pope et al observed 35% 5-year survival in patients with RCC on chronic hemodialysis vs 42% 5-year survival in patients with RCC in the general population.[3] Survival rates are more striking when the 89% 5-year survival rate in patients without RCC on chronic dialysis reported by Ishikawa et al[18] is compared to the 35% 5-year survival rate in patients with RCC on chronic hemodialysis.[3]

The benefit to screening patients with ESRD with routine imaging has been a subject of debate. Proponents argue that the costs of screening US outweigh the benefits of detecting RCC in patients on dialysis since overall survival in patients with ESRD is dictated by comorbidity risk factors. Advocates of RCC screening argue that the increased incidence of clinically significant RCC in patients on dialysis warrants screening US. We believe that screening US should be performed in all patients on dialysis after 3 years on dialysis. The 3-year point is chosen because approximately 50% of patients on dialysis have ARCD by the 3-year mark and ARCD progressively worsens as the duration of dialysis increases.[3] Before 3 years in those with ESRD the risk of RCC is presumably equal to the risk in the general population. In our study the median history of dialysis was 8 years. The longer the patient is on dialysis, the greater is the risk of RCC and the higher is the positive predictive value of screening US.

In their study Gulanikar et al reported that the sensitivity of screening US was 36.3% and the positive predictive value of a solid mass was 100%.[19] US sensitivity increases as tumor size increases. While US is more difficult in patients with multiple renal cysts, such as those with ARCD or ADPCKD, an experienced physician can readily identify solid renal masses or complex renal cysts greater than 1 cm. The cost of screening renal US is $72.[19] Screening CT remains more sensitive than US but CT is not as cost-effective as US.

Heinz-Peer et al observed that RCC in patients with ESRD grows at a rate of 0.5 to 1.0 cm yearly.[20] Since most renal tumors grow slowly and approximately half of the patients with ESRD have ARCD after 3 years on dialysis, we