

Renal Cell Carcinoma in Patients with Chronic Renal Failure

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Abstract

It has been found that patients suffering from chronic renal failure (CRF) are prone to develop acquired cystic kidney disease, which may subsequently lead to the development of renal cell carcinoma (RCC). We reviewed 250 consecutive cases of RCC diagnosed between January 1990 and June 1998 in our Department and found 19 had associated CRF (7.4%). Their clinical presentation, mode and duration of dialysis, diagnostic evaluations, pathological stage and surgical outcome were reviewed. Sixteen had CRF with chronic glomerulonephritis and 3 with adult polycystic kidney disease. Three patients were on continuous ambulatory peritoneal dialysis (CAPD), 5 were on haemodialysis (HD) and 3 had renal transplant (2 on HD, 1 on CAPD previously). The remaining 8 patients were not on renal replacement therapy at the time of diagnosis. Ten patients were asymptomatic with incidental radiological findings while 9 had specific urological symptoms, most commonly haematuria. Ultrasonography (USG) and computed tomography (CT) scan were the main modalities of imaging employed. Nine out of the 10 asymptomatic patients had suspicious lesions detected incidentally by USG. All had subsequent preoperative CT scans confirming the presence of these lesions. All patients had single focus RCC except for 1 with multi-focal disease involving both kidneys. Sixteen patients had early stage (T1 or T2) and low grade (G1 or G2) RCC. The remaining 3 patients had advanced stage (T3a or T3b) and high grade (G3) tumours. Since half of the patients were asymptomatic, USG may be a useful tool in the outpatient review of patients with CRF and allow early diagnosis and surgical treatment of early stage, low grade tumours and therefore may have better survival.

Ann Acad Med Singapore 1999; 28:512-5

Key words: Renal failure, Acquired cystic disease, Early detection, Renal cell carcinoma

Introduction

Dunnill and associates¹ first described the association of renal cell carcinoma (RCC) with acquired cystic kidney disease (ACKD) and end stage renal disease. The incidence of ACKD in dialysis patients ranges from 10% to 90% depending on the duration of dialysis.² Malignant transformation can occur in up to 8% of these patients. Terasawa et al³ recommended that haemodialysis patients should be screened by ultrasound for early detection of RCC. A retrospective analysis of all patients who developed RCC with background history of chronic renal failure (CRF) over the past 8 years at our hospital was done to establish the significance of RCC in chronic failure patients and to evaluate the efficacy of ultrasonography (USG) and computed tomography (CT) scan in the diagnosis.

Patients and Methods

The hospital records of 250 consecutive patients with RCC diagnosed between January 1990 and June 1998

were reviewed. Of these patients, 19 were found to have CRF. This included 13 male and 6 female patients with a mean age of 54.9 years (range 38 to 63 years). We evaluated their clinical presentation, mode and duration of renal replacement therapy, diagnostic imaging used, clinico-pathological stage and surgical outcome. Clinical presentation was asymptomatic when it was an incidental diagnosis by imaging only. The TNM staging classification of the International Union Against Cancer was used for staging and Fuhrman's grading was used for histological grading. The presence of any acquired cystic kidney disease was also noted. In the follow up of these patients after surgery, imaging with either CT scans or USG were employed.

During the same period, 2462 patients were involved in the haemodialysis programme, 460 in continuous ambulatory peritoneal dialysis and 320 renal transplants were performed. These 19 patients with RCC therefore came from a cohort of about 4000 patients with renal failure.

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Results

Overview

Out of the 19 patients, 16 had CRF secondary to chronic glomerulonephritis. The remaining 3 had adult polycystic kidney disease. Three patients were on continuous ambulatory peritoneal dialysis (CAPD), 5 were on haemodialysis (HD) and 3 had renal transplant (2 on HD, 1 on CAPD previously). The remaining 8 patients had not been started on renal replacement therapy at the time of diagnosis of RCC with serum creatinine ranging from 188 to 721 $\mu\text{mol/L}$. Ten patients were asymptomatic with incidental radiological diagnosis while 9 had symptoms, the commonest was haematuria. Nine of the 10 asymptomatic patients had USG as the initial incidental finding that raised the suspicion of the presence of RCC. These included 4 end stage renal failure patients (1 on dialysis, 3 transplanted patients) who were on their routine follow up. The other 6 asymptomatic patients had USG performed as part of their diagnostic work-up for their renal failure. Out of the 19 patients, 16 had diagnosis confirmed by CT scan. Unilateral nephrectomy was performed in 15 patients, bilateral in 3 and the remaining 1 patient underwent a partial nephrectomy. All the histological specimens showed RCC with the presence of glomerulonephritis as the background pathology and 9 of these had acquired cystic kidney disease. Eighteen patients had single focus disease and 1 patient had multi-focal and bilateral RCC. Clear cell carcinoma was the commonest type of RCC accounting for 52.6% of the patients. The mean size of tumour was 3.8 cm (range 1.5 to 10 cm). Of the 19 patients, only 3 had advanced stage tumours (T3a or T3b) while the other 16 had early stage tumours (T1 or T2). The 16 early stage patients also had low grade tumours (G1 or G2). In a mean follow up duration of 15.0 months, there was no evidence of tumour recurrence detected in any of the patients. There were 2 deaths but these were not due to RCC. One patient died of an acute myocardial infarction at 15 months but was disease free. The other patient died of methicillin-resistant *Staphylococcus aureus* peritonitis which occurred more than 1 month after discharge. The age of presentation of RCC in our general population ($n = 231$) was 57.0 years and only 16.8% of these patients were asymptomatic. However, 44.6% of them had tumours T3/T4 disease or had metastasis at the time of diagnosis (Table I). A summary of the clinical parameters of all the patients is tabulated in Table II.

Dialysis Group

Eight patients (6 males, 2 females) were on dialysis at the time of diagnosis. Three were on CAPD and 5 on HD. The cause of renal failure was chronic glomerulonephritis in 6 and polycystic kidney disease in 2. The mean duration of dialysis at presentation was 76.9 months. Six patients were symptomatic. Three of them had advanced

TABLE I: RENAL CELL CARCINOMA (RCC) IN THE GENERAL POPULATION AND CHRONIC RENAL FAILURE (CRF) PATIENTS

	General population $n = 231$ (Rate of 1 in 12,000)	CRF patients $n = 19$ (Rate of 1 in 210)
Age (years)	57.0	54.9, ns
% asymptomatic	16.8%	52.6%, $P < 0.05$
Advanced disease T3	44.6%	15.8%, $P < 0.05$

RCC was 57 times more in those with CRF
ns: not significant

TABLE II: CLINICAL PARAMETERS OF CHRONIC RENAL FAILURE PATIENTS WITH RENAL CELL CARCINOMA

	Dialysis ($n = 8$)	Transplant ($n = 3$)	No dialysis ($n = 8$)
Age (years)	51.8	51.3	59.5
Male /Female	6/2	3/0	4/4
Duration (months)	76.9	84.0	Not applicable
Asymptomatic presentation	2/6	3/0	6/2
Tumour size (cm)	4.0	3.2	4.2
Advanced stage	3/8	0/3	0/8
Follow up (months)	18.6	6.3	14.6

stage (T3/T4) and high grade (G3) tumours. None of the patients had lymph node involvement or metastasis at the time of presentation.

Transplant Group

Three patients had renal transplant and their renal failure was uniformly due to chronic glomerulonephritis. Two patients had been on HD and 1 on CAPD prior to transplantation. These patients had undergone a mean duration of 4.3 years of dialysis prior to transplantation. The tumours were detected at a mean of 84 months after the renal failure. All the patients had functioning graft at the time of presentation and all were chronically immunosuppressed. They were asymptomatic and had their grafts and native kidneys under regular imaging. All the tumours were early stage (T1/T2) and low grade (G1/G2). All had nephrectomy done and were still on immunosuppression with their grafts functioning. Although there was theoretically a higher chance of tumour progression in the presence of compromised immune function, it had not been so in these 3 patients.

No Renal Replacement Therapy Group

Eight patients first presented with renal impairment and had not been started on any form of renal replacement therapy at the time of diagnosis of RCC. All had renal impairment due to chronic glomerulonephritis except for 1 patient with concomitant polycystic kidney

disease. Six patients were asymptomatic. This group of patients had a mean creatinine level of 389 $\mu\text{mol/L}$ (range 188 to 721 $\mu\text{mol/L}$). They underwent USG as part of the investigation to find out the cause of renal impairment. All the patients in this group had early stage and low grade tumours.

Discussion

Since Dunnill's first description of ACKD and RCC in haemodialysis patients, there has been much interest in the natural history of ACKD and its possible malignant transformation in CRF patients.¹ Many have sought to evaluate the possible factors that may indicate an increased risk for such a transformation in this population.^{2,4,5} Radiographic surveillance for such patients has been advocated.^{3,6,7} However, justification for screening for RCC in CRF patients should be based on the following points, which include, firstly a higher rate of RCC in CRF patients compared to the general population, secondly the availability of a non-invasive and inexpensive modality of screening during follow up and thirdly an improved prognosis with early diagnosis. From our calculation shown in Table I with a total of 250 RCC patients coming from an estimated general population in Singapore of 3 million and the other 19 RCC patients coming from the group of 4000 CRF patients at the same time of the study, we can estimate that there is a 57 times more chance in CRF patients than the general population of developing RCC.

ACKD is defined as the presence of more than 3 cysts or when more than 25% of the renal parenchyma is involved with cystic changes.² Chronic renal failure is the key to the development of ACKD which begins even before the initiation of dialysis.⁸ The pathogenesis is still unclear. However, there has been some speculation of possible stimulation by a renal cell growth factor⁹ and renotropic factors¹⁰ in the presence of insufficient renal function causing hyperplastic changes and resulting in the formation of RCC. Some have suggested that renal transplantation can result in the regression of ACKD changes in the native kidneys.⁴ However, others are of the opinion that the malignant potential still exists in this group of patients and is related to the underlying cause of renal failure rather than the use of chronic immunosuppressive therapy.¹¹ The incidence of acquired cystic disease ranges from 10% to 90% depending on the period of dialysis.* It has also been found that haemodialysis and CAPD patients exhibit a similar prevalence of ACKD¹² and the primary concern is the occurrence of RCC. The rate of malignant transformation of ACKD to RCC varies throughout the literature in the range of 1% to 8%.^{1,2,5,13,14} The incidence of RCC in the general population on the other hand varies from 0.07% to 0.64%^{15,16} which were high because of awareness and early detection. In fact, Tosaka et al¹⁶ reported a rate of only 0.04%

for a general population on ultrasound screening. It has been reported that CRF patients have also an increased risk of other non-renal malignancies.^{17,18} Several reports have then suggested that the prevalence of RCC is greater in haemodialysis patients^{3,5} and in the native kidneys of renal transplant recipients^{13,14} compared to the general population. In a recent study by Doublet and associates,⁷ they estimated the risk of RCC to be as high as 100 times greater in asymptomatic renal transplant recipients versus those in the general population. Our study also showed a higher chance of 57 times.

Matson and Cohen⁸ suggested that RCC developed at the early stage in CRF patients and therefore in a younger age group. The mean age at presentation of our series of 19 CRF patients with RCC was 54.9 years and the 231 RCC from the general population was 57.0 years. The stratified values for the dialysis, transplant and no renal replacement therapy groups were 51.8 years, 51.3 years and 59.5 years, respectively. There was no difference found amongst these groups.

In recent years, there has been an increased rate of detection of RCC largely due to the widespread use of USG and CT scan.^{15,16,19} In our study, USG raised suspicion of RCC in 9 out of the 10 asymptomatic patients. Overall, USG raised suspicion of RCC in 14 out of 17 patients. Subsequently CT scan done showed good diagnostic accuracy in 16 out of 19 patients (84.2%). Terasawa and associates³ reported a 100% diagnostic rate by USG and proposed that USG was the most useful method to diagnose RCC in haemodialysis patients and that CT scan and angiography were only adjuncts. Cognny-Van Weydevelt and associates⁶ also suggested that USG was an accurate imaging for detection of RCC in renal transplant recipients. In our experience, USG was useful as the initial screening in this group of patients and when it raised any suspicion, CT scan was the next imaging modality of choice. It also provided more information about invasion and lymph node status that USG was unable to provide.

Chung and associates¹⁸ reported that patients with CRF not on renal replacement therapy yet would have ACKD at the time of diagnosis of RCC. Matson and Cohen⁸ found that 8% of the patients with end stage renal disease had ACKD at the time of initiation of dialysis. In our study series, 42.1% of CRF patients with RCC had ACKD. Therefore, in the initial assessment of CRF patients, USG is important in the detection of kidney size and hydronephrosis as well as ACKD.

Porena and associates¹⁹ suggested that incidental tumours were significantly earlier staged tumours than symptomatic tumours. In our series of 19 patients, 16 (84.2%) had early stage and low grade tumours. In a mean follow up time of 15.0 months, there were no recurrences or progression detected in these patients. The 2 deaths were not due to RCC. The follow-up period

was short for us to comment on the survival of this group of CRF patients who have developed RCC. However, it is significant that most of the tumours detected were in the early stages; 84.2% in the CRF group as compared to 55.4% in the other group with early stage at the time of diagnosis.

It was previously reported that RCCs were more aggressive in renal transplant recipients because of the compromised immune mechanism.^{20,21} In our series, all the 3 patients with advanced stage and high grade tumours belonged to the dialysis group. It might be related to a closer surveillance programme in the transplant group and the detection was therefore early. Doublet and associates⁷ suggested that there was no significant relationship between RCC and chronic immunosuppressive therapy. The 3 transplant patients with RCC all had early stage tumours and the immunosuppression was continued without progression of the RCC.

Conclusion

We should have a high index of suspicion of RCC when following up CRF patients. However, this should not only be limited to end stage renal failure patients on renal replacement therapy or transplant but also extended to those not started on renal replacement therapy. Ultrasonography is an excellent screening tool. It is inexpensive, non-invasive and easily performed in the clinic. When USG raises suspicion, then CT scan serves as an excellent diagnostic tool. This screening has resulted in the early detection of early stage and lower grade tumours. We therefore recommend that USG should be used regularly to screen patients with CRF.

Acknowledgements

We are grateful to A/Prof Woo Keng Thye, Head, Department of Renal Medicine, Singapore General Hospital for his contribution to the statistics and Ms T Punitha, Department of Urology, Singapore General Hospital for her secretarial assistance.

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