Haemodialysis related renal cell carcinoma

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ABSTRACT

Introduction: Development of renal cell carcinoma (RCC) is a life threatening complication of long-term haemodialysis. Studies have shown that approximately one third or more of patients on long-term haemodialysis of more than three years will develop acquired cystic kidney disease (ACKD), and 20-50% of patients with ACKD, particularly with complex cysts of Bosniak types IIF, III and IV, may eventually transform into RCC. This study looks at the incidence of haemodialysis related RCC in Brunei Darussalam. **Material and Methods:** Cases of RCC registered in the Department of Pathology registry from January 2000 to December 2010 were identified and retrospectively reviewed. **Results:** A total number of 5,287 malignancies were reported during this period of which 74 were RCC, giving an overall incidence of 1.4%. Out of these 74 cases, 6.8% (n=5) was found to be RCC transformed from ACKD associated with long-term haemodialysis. There was a male preponderance (4:1), four Malay men and one Chinese lady with a median age of 51 years (37-66) at diagnosis. The duration of haemodialysis prior to the development of RCC ranged from 4 to 16 years. The common presenting signs and symptoms were cystic mass in kidney 60% (n=3), haematuria and metastatic RCC in urinary bladder 20% (n=1), metastasis to the neck glands 20% (n=1). The right kidney was affected in four (80%) and one on the left (20%). **Conclusion:** Our study showed that ACKD associated RCC accounted for 6.8% of all RCC, and the duration to RCC development ranged from four to 16 years. There was a preponderance in males. Radiological screening may need to be considered for patients at risk.

Keywords: Acquired cystic kidney disease, haemodialysis, hypernephroma

INTRODUCTION

Development of renal cell carcinoma (RCC) is a life threatening complication of long-term maintenance haemodialysis for end-stage renal disease. Studies have shown that approximately one third or more of patients on long-term haemodialysis of more than three years will develop acquired cystic kidney disease (ACKD) and 20-50% will eventually develop into RCC. [1] The risk is particularly higher among those patients with complex cysts; Bosniak types IIF, III and IV. The risk of developing RCC in patients with ACKD is estimated to be fifty times higher compared to the general population. [2] This study assessed the incidence of haemodialysis related RCC in Brunei Darussalam.

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MATERIAL AND METHODS

Confirmed cases of RCC recorded in the Department of Clinical Pathology Registry, Raja Isteri Pengiran Anak Saleha (RIPAS) hospital, from January 2000 to December 2010 were identified and retrieved with the aid of Laboratory Information Service (LIS). RCC associated with gross and microscopic evidence of ACKD were selected for study, and the patients' case notes were retrieved from the Medical Record Office and reviewed in detail. Imagings of patients prior to surgery were also retrieved and reviewed.

RESULTS

The total number of all malignancies registered during the study period was 5,287, and RCC represented 1.4% (n=74). Out of 74 cases of RCC, 6.8% (n=5) was found to be long-term haemodialysis related ACKD with RCC transformation.

The patients' ages ranged from 37-66 years. A preponderance in males was observed (4 males: 1 female). All male patients were Malay and the lone female patient was a Chinese. The duration of haemodialysis prior to the development of RCC in these cases ranged from 4 to 16 years.

The common presenting symptoms were abdominal fullness or distension secondary to kidney mass (n=3, 60%), haematuria and metastatic RCC in urinary bladder (n=1, 20%), metastatic RCC to the neck glands (n=1, 20%).

Grossly, the kidneys were multi-cystic in appearance. Renal weight and sizes varied from 70 to 300gms and 8.5 to 22cm in greatest dimension respectively. The cysts varied in sizes from 1.5 to 3cm in diameters. Representative gross morphology of acquired cystic kidney (Case 4) is illustrated in Figures 1.

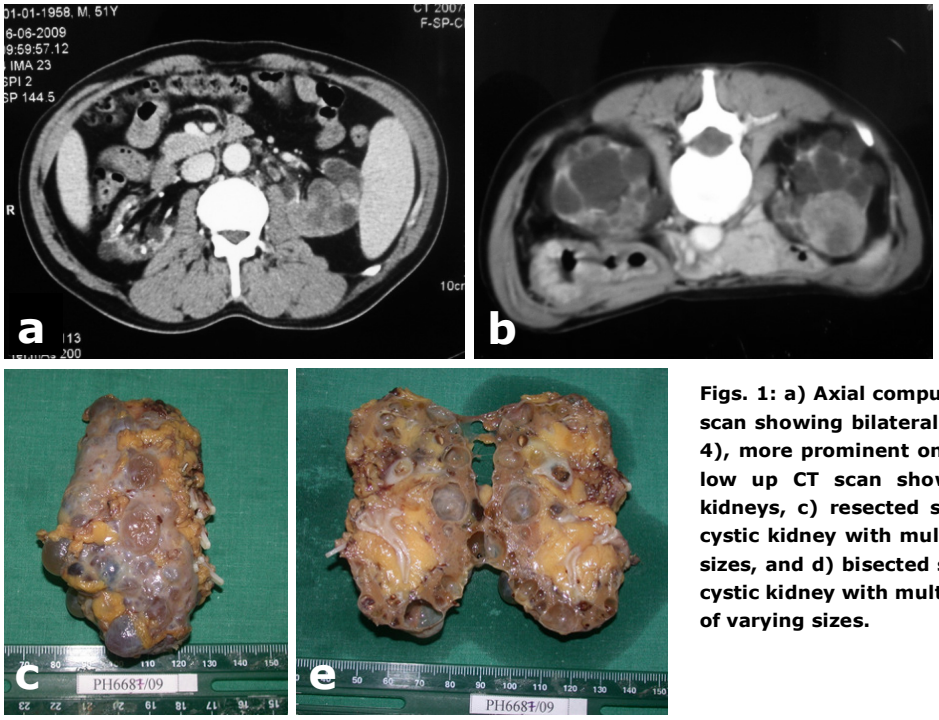
Histologically, all cases showed features of ACKD progressing into RCC. The cysts were lined by layer of benign flat to low cuboidal epithelium to atypical hyperplasia to papillary in-situ carcinomatous change and early invasion of cyst walls. These histologic features of ACKD and early carcinomatous changes were illustrated in Figures 2.

DISCUSSION

The development of RCC is a serious but rare complication in patients undergoing long-term maintenance haemodialysis. In general, RCC is responsible for a small percentage of total cancer cases and accounts for nearly two per cent of all malignancies globally. [3, 4] In our study period, RCC constituted 1.4% of all malignancies and only five cases (6.8%) were associated with long-term haemodialysis, es-

Table 1: Summary of the cases of renal cell carcinoma associated with haemodialysis.

Case	Age/gender	Race	Duration of HD	Presentation	ACKD	RCC	Histology
1	37/M	Malay	16 years	Abdominal mass	Right	Right	Conventional RCC
2	54/M	Malay	4 years	Pain	Right	Right	Papillary RCC
3	49/F	Chinese	7 years	Metastasis (neck lymph nodes)	Right	Right	Papillary chromophil RCC with sarcomatoid pattern
4	51/M	Malay	16 years	Metastasis (bladder)	Right	Right	Multicystic RCC
5	66/M	Malay	4 years	Abdominal mass	Both	Left	Cystic papillary RCC

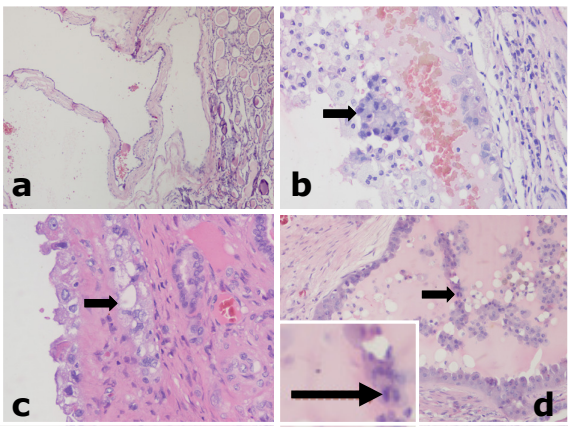


Figs. 1: a) Axial computed tomography (CT) scan showing bilateral cystic kidneys (Case 4), more prominent on the left side, b) follow up CT scan showing bilateral cystic kidneys, c) resected specimen of acquired cystic kidney with multiple cysts of varying sizes, and d) bisected specimen of acquired cystic kidney with multiple cysts of varying sizes.

sentially similar to reported global incidence of RCC. [3, 4]

There was a male preponderance and the median age of our patients was 51 years (range 37 to 66). Most of our patients were Malay and this is consistent with our haemodialysis and the national population demographics. The duration of haemodialysis among our patients ranged from four to 16 years with a median of seven years. This is consistent with what has been reported earlier with most transformations occurring after years of haemodialysis. [1]

The development of RCC from ACKD is a continuous process with damage to renal tubules and resultant formation of simple cysts lined by non-neoplastic tubular epithelial cells. The latter in some of the cysts may progress into hyperplasia to atypical hyperplasia to adenomatous changes and finally RCC transformation. The pathogenesis of this continuous process is not definitely known but growth factor-induced compensatory proliferative tubular epithelium initiated by changes



Figs. 2: a) Microphotograph of acquired cystic kidney showing cysts lined by flattened to low cuboidal epithelium (Stain, H&E, x20) (Case 4), b) in-situ papillary carcinomatous change and detached papillae within the lumen (arrow) (H&E, x40), c) A cyst with in-situ papillary carcinomatous change and detached papillary cluster within the lumen (arrow) (H&E, x40), and d) in-situ papillary carcinomatous change and early invasion of adjacent renal interstitial tissue (arrow) (H&E, x40), magnified image (insert).

of ESRD in the uraemic milieu and probably perpetuated by proto-oncogenes seems to be the most plausible pathogenetic factor. [2] The loss of function of connexin (CX) 32, a member of gap junction, a potential tumour suppressor gene; during long term maintenance haemodialysis may also play an important role in the pathogenesis of dialysis related ACKD with transformation into RCC. [5]

It has been estimated that there is a 50 fold or more increased risk for RCC in patients with long-term haemodialysis compared to the general population. [2, 6] This is higher in patients who have already developed ACKD from long-term haemodialysis. With the increase in the number of patients with chronic kidney disease requiring dialysis, coupled with the increase in the survival of chronic dialysis patients, the number of RCC associated with ACKD will be expected to increase, albeit a small increase for a small country like Brunei Darussalam. A screening programme for early detection of asymptomatic ACKD and RCC by radiological imaging studies, such as routine interval ultrasonography and CT may need to be considered, taking into account patients' demographics that place them at higher risk. However, recommendations for screening of ESRD patients for ACKD and RCC remain highly controversial. [1, 2, 6-9]

In conclusion, our study showed that 6.8% of RCC were associated with long-term haemodialysis. Our study serves as "food for thought" for the consideration of initiation and establishment of a screening programme for patients with ESRD on long-term maintenance haemodialysis taking into account patients' risk factors, expected survival and or renal transplantation status.

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