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ORIGINAL ARTICLE

High incidence of urinary tract malignancy among patients with haematuria following kidney transplantation in Taiwan

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Summary

Haematuria is a common complication following kidney transplantation, but few studies describing post-transplant haematuria have been published. Herein, we investigated the incidence and etiologies of persistent hematuria with kidney transplant patients in Taiwan. The medical records of 189 kidney transplant recipients with functioning grafts were retrospectively reviewed. Any episode of haematuria during routine follow-up was recorded and evaluated. The patient characteristics, possible causes of haematuria and consequent managements were reviewed. Among the 189 patients, 44 patients (23.3%) experienced 45 episodes of persistent haematuria during routine monthly follow-up at our transplant clinic. Thirty-two episodes (71%) were microscopic haematuria and 13 (29%) were gross haematuria. The most prevalent etiology explained for the persistent haematuria in our series was urologic malignancy (19 patients, 42.2%), followed by urinary tract infections (24.5%) and unexplained reasons (17.8%). Furthermore, those patients with persistent haematuria caused by urologic malignancy were also associated with significantly longer duration following transplantation and worse graft function. Haematuria is frequently seen in kidney transplant recipients and the most prevalent cause in our series is urologic malignancy. Those patients were also associated with significantly poorer graft function; however, the mechanism is still unclear.

Introduction

Haematuria following kidney transplantation was first addressed by Previte *et al.* in 1978. They reported an incidence of 12% in 127 male kidney transplant recipients and inflammatory conditions accounted for half of the cases. Three patients with acute rejection episodes also presented with gross haematuria, but no urological malignancy was found in their series [1]. In 2002, Butani *et al.* evaluated 21 paediatric Kidney transplant recipients and seven (33%) had persistent microscopic haematuria. The possible causes explained for the microscopic haematuria included intermittent bladder catheterization, recurrent IgA nephropathy, cytomegalovirus (CMV) nephritis and unexplained reasons [2].

A more extensive cross-sectional study enrolled 640 kidney transplant recipients for dipstick urinalysis. The prevalence of persistent dipstick haematuria was 13.3%. Major identified causes included chronic urinary tract infection, persistent menstrual bleeding, anticoagulant therapy, recurrent or de novo glomerular diseases and chronic allograft nephropathy. Allograft renal cell carcinoma was diagnosed in one patient and was managed with partial graft nephrectomy. In addition, they concluded that patients with haematuria had poorer graft function and higher risk to progress to graft failure [3].

The most detrimental cause of haematuria is urological malignancy and kidney transplant recipients in Taiwan are predisposed to develop urothelial carcinoma (UC) of native urinary tracts [4–7]. Given these observations,

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complete evaluation for these patients with either microscopic or macroscopic haematuria during routine transplant follow-up is crucial. Therefore, the objective of our study is to investigate the prevalence, possible aetiologies and management of haematuria in patients at our kidney transplant clinic in Taiwan.

Materials and methods

We retrospectively reviewed the medical records of kidney transplant recipients who have been followed up at or transferred to the transplant clinic of Department of Urology of National Taiwan University Hospital from 1997 to 2007. The inclusion criteria included: (i) patients with active follow-up at our clinic, (ii) patients with functioning grafts at least 3 months after transplantation, and (iii) patients without history of urological and gynaecological malignancy before kidney transplantation. No organ donors were from executed prisoners and our programme adhered to the Transplantation Society Guidelines. One hundred and eighty-nine patients were eligible for our study.

All patients were followed up at least monthly at our kidney transplant clinic. Complete blood count, renal/liver function tests, lipid profile, immunosuppressive drug levels and urinalysis (both dipstick and microscopic examination of urine sediment) were monitored periodically.

Any episode of isolated haematuria (haematuria without proteinuria or casts) at each visit was recorded. Persistent or significant haematuria was defined as the presence of >3 red blood cells per high-power field (HPF) on three consecutive urinalyses on three different days, or a single urinalysis with >100 RBCs/HPF on a centrifuged urine specimen under microscopic examinations, or gross haematuria.

Initial evaluation of patients with haematuria consisted of routine bacteriology, urine cytology and urological ultrasound (including urinary bladder, native and graft kidneys). Imaging studies including retrograde pyelography, computed tomography or magnetic resonance imaging were arranged for high risk patients, for instance, patients with hydronephrotic native kidney or abnormal urine cytology result. Finally, endourological examinations (cystoscopy/ureteroscopy) were used to confirm the diagnosis. Persistent haematuria from the same or unexplained causes after complete work-up was excluded from further data collection and analysis.

The data in this study were expressed as the mean ± the standard error of mean. The comparison between the two groups was made by chi-squared test or independent Student's test. A P-value of <0.05 was considered statistically significant. All analyses were performed with Statistical Package for the Social Science software (SPSS 13th ed., Chicago, IL, USA).

Results

A total of 45 episodes of persistent haematuria were recorded in 44 patients (23.3%) during routine monthly follow-up at our transplant clinic. Thirty-two episodes (71%) were microscopic haematuria and 13 (29%) were gross haematuria. The median duration from kidney transplantation to the first episodes of haematuria was 30 months (5–96). The baseline patient characteristics were listed in Table 1. The mean age at kidney transplantation was 44.1 ± 1.5 years for haematuria group and 41.9 ± 0.9 years for nonhaematuria group (NH group) ($P = 0.29$). Of the 189 kidney transplant recipients, 80 patients (42%) were men and 109 (58%) were women. There was no significant difference in age at transplantation and gender distribution between the two groups ($P = 0.29$ and 0.77, respectively).The initial graft function after kidney transplantation was also comparable ($P = 0.76$). However, the haematuria group had less living related donor transplantation (4.4% vs. 21.4%, $P < 0.05$) and longer duration following transplantation (5.9 ± 0.6 vs. 4.5 ± 0.3 years, $P < 0.05$). Furthermore, the haematuria group was associated with significantly poorer graft function (1.78 ± 0.13 vs. 1.46 ± 0.05 mg/dl, $P < 0.05$) than the NH group. However, there was no difference regarding the incidence of acute rejection episodes

Table 1. Baseline characteristics of kidney transplant recipients with or without persistent haematuria.

	Haematuria group (n = 44)	Nonhaematuria group (n = 145)	P-value
Age at KT (years)	44.1 ± 1.5 (23–63)	41.9 ± 0.9 (15–71)	0.29
Male (%)	18 (41)	64 (44)	0.77
LRD KT (%)	2 (4.4)	31 (21.4)	<0.05
Time since KT (years)	5.9 ± 0.6 (0.8–16)	4.5 ± 0.3 (0.6–20)	<0.05
Serum creatinine (mg/dl) after KT	1.23 ± 0.06 (0.8–2.4)	1.25 ± 0.03 (0.8–2.2)	0.76
Serum creatinine (mg/dl) at present	1.78 ± 0.13 (0.8–4.8)	1.46 ± 0.05 (0.7–5.4)	<0.05
Patients with γ 1 AR episode(s) (%)	12 (29.5)	40 (27.5)	0.80

KT, kidney transplantation; LRD, living related donor; AR, acute rejection.

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Table 2. Possible causes of original stage 5 chronic kidney disease (CKD) in 44 patients with persistent haematuria.

Causes of CKD stage 5	Patient no.
Glomerulonephritis	9
Diabetes	1
Hypertensive nephrosclerosis	2
Obstructive uropathy	2
Polycystic kidney disease	1
Drug-related	3
Toxaemia	1
IgA nephropathy	1
Unknown	24

Table 3. Potential aetiologies of 45 episodes of persistent haematuria.

Potential aetiology	Episodes no. (%)
Urinary tract infection	11 (24.5)
Urinary tract malignancy	19 (42.2)
Urolithiasis	2 (4.4)
Chronic inflammation	2 (4.4)
Graft ureteral stent	1 (2.2)
IgA nephropathy	1 (2.2)
Interstitial nephritis	1 (2.2)
Unexplained	8 (17.8)
Total	45

between the two groups (29.5% vs. 27.5%, $P = 0.80$). The possible causes of original stage 5 chronic kidney disease in the 44 patients with persistent haematuria are listed in Table 2.

The potential aetiologies explained for persistent haematuria included 11 urinary tract infections (24.5%), 19 urinary tract malignancies (42.2%), two urolithiasis (4.4%), two chronic cystitis (cystitis glandularis, 4.4%), three miscellaneous causes (6.7%, IgA nephropathy, intersitital nephritis and graft ureteral stent) and eight unexplained causes (17.8%). The possible causes of persistent haematuria are summarized in Table 3.

We further stratified the haematuria group into two distinct subgroups: malignant haematuria group (MH group) and benign haematuria group (BH group) and compared several parameters among the NH group, MH group and BH group. We found that the NH and BH groups were comparable in age at transplantation, gender, duration after transplantation and serum creatinine level. However, the MH group had significantly longer duration following transplantation and higher serum creatinine level than the NH and BH groups. The comparison among NH, MH and BH groups is shown in Table 4.

Discussion

Blood in urine can originate from any site along the urinary tract, including the graft kidney unit in the kidney transplant recipient. As in the general population, haematuria in the kidney transplant recipients can result from several medical and surgical problems, covering a spectrum from minor incidental findings to life-threatening conditions. However, haematuria in the kidney transplantation recipients is much more complicated. Besides the impact of immunosuppressive agents, the pelvic transplanted graft kidney seems more susceptible to trauma, stone disease and urinary tract infection than the native kidneys because of its anatomical alteration [8–10].

Only few reports describing the frequency and possible causes of haematuria following kidney transplantation have been published in the literature [1–3]. In contrast to the previous reports, in which a majority of causes identified were associated with nonmalignant conditions, the most prevalent cause contributing to persistent haematuria in our series was urological malignancy (42.2%) including one superficial bladder UC, one invasive bladder UC, 16 patients with upper urinary tract UC (ureter/renal pelvis) and one adenocarcinoma of urachus. All the tumours were identified in the native urinary tracts. For kidney transplant recipients with urinary tract UC, we performed bilateral nephroureterectomy with

Table 4. Comparison among NH, MH and BH groups.

	NH group (n = 145)	MH group (n = 18)*	BH group (n = 25)*	P-value
Age at KT (years)	41.9 ± 0.9	45.5 ± 2.3	42.4 ± 2.1	NS
Male (%)	64 (44)	7 (39)	11 (44)	NS
Time since KT (years)	4.5 ± 0.3	7.4 ± 1.1	5.1 ± 0.6	<0.05†
Serum creatinine (mg/dl) at present	1.46 ± 0.05	2.1 ± 0.27	1.52 ± 0.11	<0.05†

KT, kidney transplantation; NH, nonhaematuria group; MH, malignant haematuria group; BH, benign haematuria group; NS, not significant.
*One patient had both episodes of MH and BH was excluded from the analysis.
†Between the MH group and NH/BH groups.

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bladder cuff excision for native kidneys. For superficial bladder cancer, the standard treatment was transurethral resection and intravescial chemotherapy. For invasive bladder cancer, lateral nephroureterectomy, radical cystectomy and subsequent graft percutaneous nephrostomy as urinary diversion were performed. Of note, we performed partial cystectomy and enterovesicoplasty for the patient with urachal adenocarcinoma. Among them, six patients (31.5%) presented with microscopic haematuria and more than half (52.6%) of the patients were accompanied by chronic urinary tract infection.

One patient had graft ureteral calculus presented with obstructive uropathy and persisted microscopic haematuria. A combination therapy of percutaneous ureterolithotripsy, shock wave lithotripsy and ureteroscopic lithotripsy was performed to achieve stone-free status. Another kidney transplant recipient had persisted microscopic haematuria for months. No evidence of malignancy was identified after thorough endoscopic and radiographic examinations. However, we still performed bilateral radical nephroureterectomy with bladder cuff excision for him and the pathological finding was squamous metaplasia possibly caused by calculus in the renal pelvis.

Compared to gross haematuria, which generally prompts a patient to seek medical attention, microscopic haematuria is often recognized by the physicians. The prevalence of asymptomatic microscopic haematuria in general population varies from 0.19% to 16.1% [11] depending on the population screened. Evaluations of microscopic haematuria have resulted in the discovery of significant disease in 3.4–56% of individuals and in the discovery of malignancy in 0–26% of individuals [12–14]. In our series, microscopic haematuria resulted from significant diseases were identified in nine cases (4.8%), including six patients with malignancy, two with calculi and one having IgA nephropathy.

Our series demonstrated that patients with haematuria caused by malignancy had significantly longer duration following transplantation and worse graft function than the patients with benign haematuria and patients without persistent haematuria. No published report has addressed the correlation between the length of duration following kidney transplantation and the risks for developing post-transplant malignancy and the allograft function in kidney transplant recipients with malignancy. It is difficult to draw definite conclusion from our limited cases. Although there are many factors contributing to impaired graft function in kidney transplant recipients with malignancy, a reasonable postulation is minimization of immunosuppressive agents after diagnosis to prevent cancer progression or recurrence. This manoeuvre may affect the graft function even though the acute rejection rate was similar among the three groups ($P = 0.58$).

Our study had some limitations. First, the definition of persistent haematuria was arbitrary and retrospective as it was not cost-effective to evaluate every single episode of haematuria during routine clinical follow-up. Furthermore, this definition needed to be examined for its sensitivity and specificity. Third, some conditions potentially contributing to post-transplant haematuria, such as CMV infection or acute rejection, were not evaluated in our series.

Conclusion

Haematuria is a common complication following kidney transplantation. At our transplant clinic in Taiwan, the most prevalent aetiology explained for haematuria after kidney transplantation is urological malignancy (>40%) followed by urinary tract infection. Kidney transplant recipients with malignant haematuria are also associated with worse graft function; however, the mechanism is still unclear.

Authorship

H-CT: collected the data, did the analysis, and wrote the initial draft. M-KL and S-MW: performed the surgery, and revised the article. S-CC: performed the surgery, and critically revised the article and is responsible for the correspondence of this article. H-JY: assisted the surgery, and helped to coordinate the study.

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