Sterile Leukocyturia Predicts Interstitial Fibrosis and Tubular Atrophy in kidney Allograft Protocol Biopsies

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Introduction

Interstitial fibrosis and tubular atrophy (IF/TA) constitute one of the most important histopathological entities associated with long-term renal allograft failure in protocol biopsies taken early after renal transplantation.

An early diagnosis of IF/TA is important given its negative impact on renal graft prognosis and its often unpredictable development due to the multifactorial etiology.

We aimed to investigate whether a routine urinalysis could predict subclinical histopathological changes in protocol biopsies with important impact in prognosis. Specifically, we hypothesized that sterile leukocyturia could be associated with Banff criteria histological findings, as a marker of inflammation.

Methods

Retrospective review of kidney transplant patients between 2006-2010 with a 6 month protocol biopsy who had an available urine sample between two months before or one month after the protocol biopsy. Patients who had a concomitant positive urine culture were excluded (Fig 1).
Renal lesions were graded and diagnosed according to the 2007 Banff update of Banff 1997 diagnostic criteria. IF/TA was defined as tubular atrophy and interstitial fibrosis in >5% in the cortical area.

Statistics
Groups were compared using the chi-square test, t-test or Mann–Whitney U-test when applied. Logistic regression analysis was used.
Cumulative percent graft and patient survival was estimated by Kaplan–Meier analysis. All statistics were performed with SPSS version 20.0.

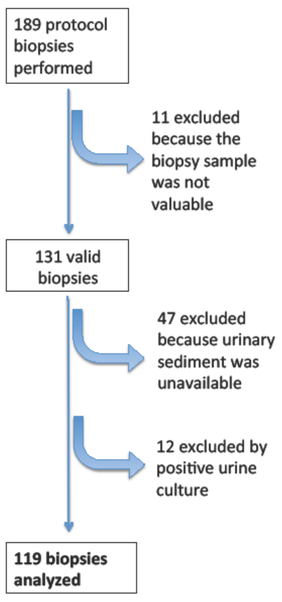

Fig1- Study population

Results

Patient characteristics: leukocyturia

	All patients (N=119)	With leucocituria (N=24)	Without leucocituria (N=95)	P
Recipient sex (male/female)	80/39	11/13	69/26	**0.012**
Recipient age (mean, SD)	49.4 (SD 12.7)	54.2 (SD 11.6)	48.2 (SD 12.8)	0.156
Donor sex (male/female)	82/36	14/10	68/26	0.183
Donor age (mean, SD)	47.9 (SD 15.3)	52.4 (SD 15.4)	46.7 (SD 15.2)	0.105
BMI (mean, SD)	25.0 (4.3)	26.9 (5.0)	24.5 (3.9)	0.068
Re-transplantation (%)	8 (6.7)	0	8 (8.4)	0.141
DD/LRD (%)	110/9	24/0	86/9	**0.001**
HLA-A MM (SD)	1.38 (0.6)	1.57 (0.6)	1.33 (0.6)	0.978
HLA-B MM (SD)	1.36 (0.5)	1.43 (0.5)	1.34 (0.5)	0.994
HLA-DR MM (SD)	0.91 (0.6)	0.78 (0.6)	0.94 (0.6)	0.230
Cold ischemia time (SD)	17.83 (7.7)	20.23 (8.6)	17.23 (7.4)	0.867
DGF (%)	26 (21.8)	9 (37.5)	15 (62.5)	**0.001**
Acute rejection (%)	18 (15.1)	3 (12.5)	15 (15.8)	0.413
Dialysis time (mean, SD)	30.1 (SD 29.5)	29.9 (26.6)	30.1 (30.3)	0.977
Induction therapy (%)	97 (82.2)	19 (79.2)	78 (83.0)	0.663
CNI (%)	83 (69.7)	16 (66.7)	67 (70.5)	0.713

Table 1a

Time of biopsy (yr)	217.5 (96.9)	236.4 (129.6)	212.7 (86.9)	0.285
Acute rejection (%)	12 (10.1)	2 (8.3)	10 (10.5)	0.750
Borderline rejection (%)	54 (45.4)	9 (37.5)	45 (47.4)	0.569
IFTA (%)	65 (54.6)	18 (75.0)	47 (49.5)	**0.025**

Table 1b

Hematuria (%)	44 (37.0)	13 (54.2)	31 (32.6)	0.051
Proteinuria, >0.15g/dia (%)	70 (68.0)	17 (81.0)	53 (54.6)	0.195
Proteinuria, >0.5g/dia (%)	10 (9.7)	5 (23.8)	5 (6.1)	**0.014**
SCr (SD)	126.3 (38.1)	123.29 (49.8)	127.05 (34.8)	0.668

Table 1c

Table 1. Main characteristics of patients with and without leukocyturia. Table 1a, Demographic and clinical data at transplant; Table 1b, Kidney protocol biopsy histology; Table 1c, Laboratory characteristics at protocol biopsy time.

Patient characteristics: IF/TA

	All patients (N=119)	With IFTA (N=24)	Without IFTA (N=95)	P
Recipient sex (male/female)	80/39	41/24	39/15	0.290
Recipient age (mean, SD)	49.4 (12.7)	51.2 (13.1)	46.6 (11.7)	**0.025**
Donor sex (male/female)	82/36	47/18	36/18	0.462
Donor age (mean, SD)	47.9 (SD 15.3)	51.9 (15.9)	43.8 (13.3)	**0.003**
BMI (mean, SD)	25.0 (4.3)	25.0 (4.3)	25.0 (4.2)	0.928
Re-transplantation (%)	8 (6.7)	2 (3.1)	6 (11.1)	0.081
DD/LRD	110/9	62/3	48/6	0.182
HLA-A MM (SD)	1.38 (0.6)	1.45 (0.6)	1.28 (0.6)	0.125
HLA-B MM (SD)	1.36 (0.5)	1.37 (0.5)	1.33 (0.6)	0.723
HLA-DR MM (SD)	0.91 (0.6)	1.02 (0.5)	0.81 (0.6)	0.062
Cold ischemia time (SD)	17.83 (7.7)	18.67 (7.3)	16.83 (8.1)	0.199
DGF (%)	26 (21.8)	19 (29.2)	7 (13.0)	**0.033**
Acute rejection (%)	18 (15.1)	13 (20.0)	5 (9.3)	0.104
Dialysis time (mean, SD)	30.1 (SD 29.5)	30.2 (29.6)	29.9 (29.7)	0.969
Induction therapy (%)	97 (82.2)	55 (85.9)	42 (77.8)	0.248
CNI (%)	83 (69.7)	46 (70.8)	37 (68.5)	0.790

Table 2a

Time of biopsy (yr)	217.5 (96.9)	205.9 (97.9)	231.4 (94.6)	0.263
Acute rejection (%)	12 (10.1)	7 (10.8)	5 (9.3)	0.785
Borderline rejection (%)	54 (45.4)	22 (40.7)	32 (49.2)	0.550

Table 2b

Hematuria (%)	44 (37.0)	26 (40.0)	18 (33.3)	0.453
Leucocituria (%)	24 (20.2)	18 (27.7)	6 (11.1)	**0.025**
Proteinuria, >0.15g/dia (%)	70 (68.0)	42 (73.7)	28 (60.9)	0.166
Proteinuria, >0.5g/dia (%)	10 (9.7)	6 (10.5)	4 (8.7)	0.755
SCr (SD)	126.3 (38.1)	132.3 (41.3)	119.0 (32.8)	0.057

Table 2c

Table 2. Main characteristics of patients with and without IF/TA. Table 2a, Demographic and clinical data at transplant; Table 2b, Kidney protocol biopsy histology; Table 2c, Laboratory characteristics at protocol biopsy time.

SD, standard deviation; BMI, body mass index; DD, deceased donor; LRD, live related donor; HLA, human leukocyte antigen; MM, mismatch; DGF, delayed graft function; CNI, calcineurin inhibitor; IF/TA, interstitial fibrosis and tubular atrophy; SCr, serum creatinine

Renal and patient survival

Fig 2a

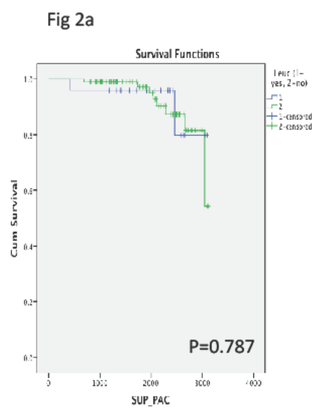

Fig 2b

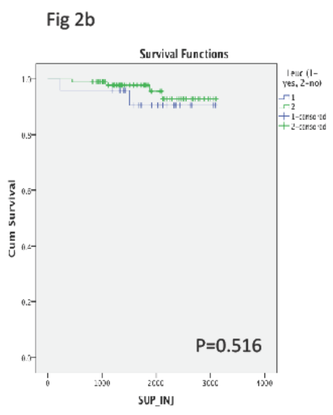

Fig 2- Patient (2a) and renal (2b) survival of patients with and without leukocyturia.

Fig 3a

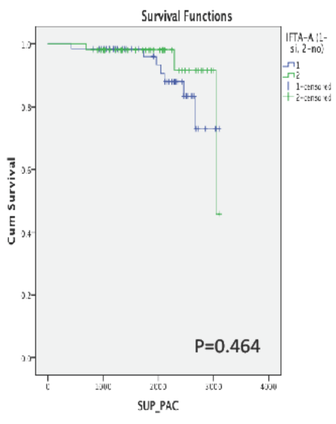

Fig 3b

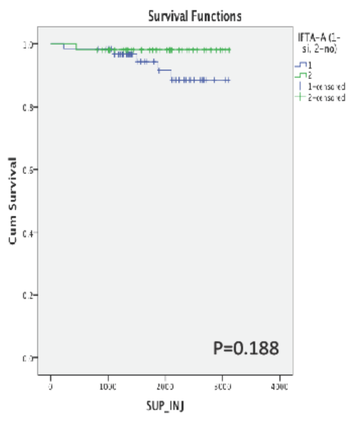

Fig 3- Patient (3a) and renal (3b) survival of patients with and without IF/TA.

Performance of leukocyturia for IF/TA prediction

	OR	P
Donor age	1.036	0.009
Leucocituria	2.74	0.050

Table 3- By multivariate analysis, only donor age and leukocyturia at protocol biopsy time predicted IF/TA

	IT/FA
Sensitivity of leucocituria	28%
Specificity of leucocituria	89%

Table 4- Sensitivity and specificity of leukocyturia for IF/TA

	IF/TA probability
Leucocituria + donor age ≥60y	90%
No leucocituria + donor age <60y	40%

Table 5- Probability of IF/TA based on leukocyturia and donor age

Conclusions

- Leukocyturia is associated with female recipients, deceased donors, delayed graft function and IF/TA on protocol biopsies
- IF/TA on protocol biopsies is associated with increased donor and recipient age, delayed graft function and presence of leukocyturia
- leukocyturia can help predict the presence of IF/TA, mainly when interpreted with donor age
- In the current omics era our results suggest that classical urinary sediment still provides valuable clinical information for the follow-up of kidney allograft recipients.

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