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Graft Microthrombus Formation in Postreperfusion Biopsies: Comprehensive Morphologic Characterization and Impact on Graft Outcome

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INTRODUCTION

Microthrombi are occasionally observed in the preimplantation and postreperfusion (MTP) biopsies of kidney donors. Considering that MTP is quite unusual, there are only a few relevant studies, leaving behind controversy and uncertainty. The pathogenesis of MTP is unclear, culminating in the most recent suggestion, with limited supporting evidence, that the endothelial injury during surgery is responsible for or at least aggravates thrombus formation.[1] The impact of MTP on graft outcome remains nebulous. We have anecdotally observed graft loss preceded by diffuse MTP on long-term follow-up, raising the hypothesis that MTP is not a merely innocent bystander, however, can promote graft loss by hitherto undetermined factors or pathways.[2–4]

Against this background of limited insight into MTP, we wished to study MTP in a systematic and comprehensive fashion, by utilizing precise morphologic techniques to probe the MTP, and harnessing the power of repeated biopsies and long-term follow-up to evaluate the impact of MTP on graft outcome and explore the factors controlling these outcomes.

RESULTS

Among 1431 renal transplant recipients between 2010 and 2016, 43 had microthrombi in the postreperfusion renal transplant biopsies (Supplementary Table S1). Glomerular thrombi were noted in each of these biopsies, which mostly affected a few glomeruli (1–3 glomeruli among a mean of 40 glomeruli seen in each biopsy). Eight biopsies had microthrombi in several glomeruli (>20%), whereas 3 had microthrombi in almost all the glomeruli. These 3 biopsies also had thrombi in peritubular capillaries whereas 1 had thrombi in the arterioles. Thrombi in the peritubular capillaries or arterioles were not noted in the absence of glomerular thrombi, in any of the biopsies.

Glomeruli and vessels with thrombi were identified by subendothelial accumulation of platelet and fibrin along with cellular debris causing luminal occlusion. Light microscopy highlighted the thrombi in all the vessels, as pale eosinophilic fibrinous subendothelial deposits in hematoxylin and eosin stain, which stained magenta color in periodic acid-Schiff, and fuchsinophilic in trichrome stain. Immunohistochemistry stain for platelets by CD61a helped especially in the identification and quantification of fibrin thrombi in peritubular capillaries. Ultrastructure excluded equivocal cases and facilitated the study of thrombi with subendothelial exclusion of accumulation of platelets, fibrin, and cellular debris occluding the lumen (Figure 1).

Glomerular sclerosis, tubular atrophy, interstitial fibrosis, and arterial intimal fibrosis were quantified in the index (postreperfusion) as well as in the follow-up biopsies. Among the 23 patients with repeat biopsies, 3

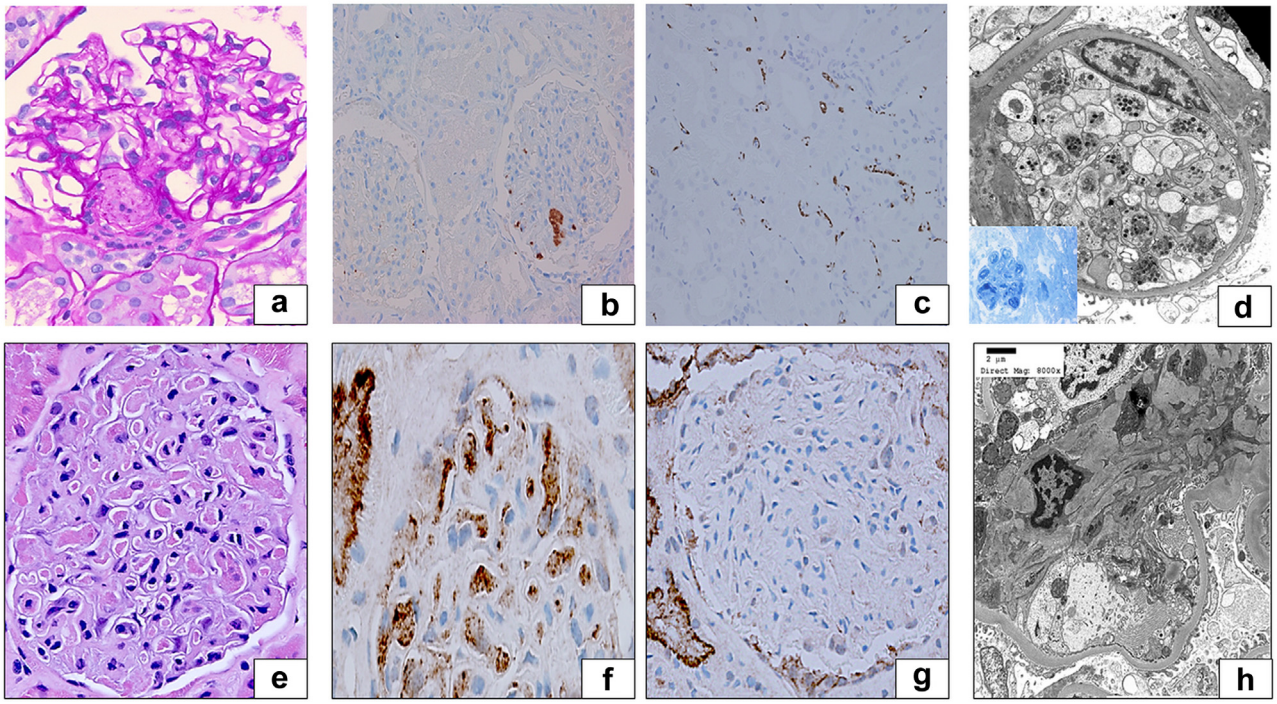

Figure 1. (a) Renal cortex with glomerular capillary lumens occluded by thrombi highlighted by the periodic acid-Schiff stain, ×200; (b) an occasional glomerular capillary with fibrin thrombi highlighted by immunohistochemical stain for CD61a, ×200; (c) peritubular capillaries from the same biopsy focus with fibrin thrombi highlighted by immunohistochemical stain for CD61a, a marker for platelet, ×200; (d) electron microscopy highlights a microthrombus composed mostly of aggregated platelets, ×8000; (inset) Toluidine blue-stained thick section demonstrating thrombi in the glomerulus subjected to electron microscopy ×400; (e) glomerular capillaries occluded by fragments of tubular epithelial cells with occasional degenerate nuclear fragments, periodic acid-Schiff stain, ×400; (f) tubular epithelial cell fragments within glomerular capillary lumens, revealed by immunohistochemical stain for RCC marker, a specific marker for tubular cell brush border, ×400; (g) these structures are not seen in an unaffected glomerulus adjacent to the one illustrated in 3B ×400; (h) electron microscopy shows fragments of tubular cells including brush border and endoplasmic reticulum in capillary lumen, ×8000.

had acute cellular rejection and 2 of them had chronic active antibody mediated injury. Two of these patients with rejection had noncompliance with immunosuppressive medications. Rejection episodes were diagnosed at 64-months, 96-months, and 100-months posttransplant, respectively. Progressive scarring of the renal cortex with >10% increase in scarring of the glomerular, tubular, interstitial, or vascular compartments in comparison with the index biopsy was observed in 7 patients.

Only 1 of the patients in the diffuse thrombi group (>20%) had persistent microthrombi on repeat biopsy. However, this patient had thrombi in all glomeruli in the index biopsy, along with thrombi in peritubular capillaries as well as arterioles and focal cortical necrosis. However, the repeat biopsy showed microthrombi only in rare glomeruli.

Donor Profiles

There was no significant association with any potential risk factor. On comparison with propensity-matched controls, donor hypertension (*P*-value 0.01) was significantly associated with MTP group (Supplementary Table S2)

Recipient Profiles

One patient each had simultaneous liver and kidney transplant, and kidney and pancreas transplants; whereas 1 had a second kidney transplant, and 1 had a fourth kidney transplant.

The recipient profiles for the MTP group and the overall non-MTP control and propensity-matched control groups are summarized in Supplementary Tables 1 and 2, respectively. Many characteristics, potentially pertinent to the pathogenesis of thrombi, as well as its impact on graft outcomes were selected for comparison between these 2 groups, but statistically significant differences were not observed in any.

Graft Outcomes and Clinicopathologic Comparisons

At "up-to-date" follow-up with a median duration of 6.8 years, 12 recipients had died of septicemia (most common), malignancy, or cardiovascular complication, with a failed graft in 6 of the 12 recipients (50%). Overall, 8 patients had graft failure at the end of follow-up. Graft failure risk analysis of the MTP group and matched control group highlighted statistically

Table 1. Correlation of donor and recipient characteristics with graft failure recipient and donor characteristics in MTP cohort, by composite event of death-censored graft failure or eGFR <30 ml/min per 1.73 m^2

	1.1. Composite event (of death-censored graft failure)			
Demographic and clinical characteristics	**Total (N = 43)**	**No event (n = 35)**	**Event (n = 8)**	***P*-value**
Recipient demographic and clinical characteristics				
Age at transplant (yr), median (IQR)	50.0 (39.0, 60.0)	52.0 (38.0, 63.0)	49.5 (46.0, 56.0)	0.91
Male gender, *n* (%)	24 (55.8)	22 (62.9)	2 (25.0)	0.11
Race/Ethnicity, *n* (%)				0.65
Non-Hispanic (NH) White	16 (37.2)	14 (40.0)	2 (25.0)	
NH Black	14 (32.6)	10 (28.6)	4 (50.0)	
Hispanic	9 (20.9)	7 (20.0)	2 (25.0)	
NH Asian	4 (9.3)	4 (11.4)	0 (0.0)	
Race/Ethnicity-NH White, *n* (%)	16 (37.2)	14 (40.0)	2 (25.0)	0.69
BMI, median (IQR)	27.6 (23.9, 32.0)	27.6 (23.6, 32.9)	27.3 (24.0, 31.3)	0.93
Malignancy, *n* (%)	4 (9.3)	4 (11.4)	0 (0.0)	1.00
Retransplant, *n* (%)	3 (7.0)	3 (8.6)	0 (0.0)	1.00
Multiorgan transplant, *n* (%)	3 (7.0)	2 (5.7)	1 (12.5)	0.47
ABO blood group				0.75
A	13 (30.2)	10 (28.6)	3 (37.5)	
B	8 (18.6)	6 (17.1)	2 (25.0)	
AB	4 (9.3)	4 (11.4)	0 (0.0)	
O	18 (41.9)	15 (42.9)	3 (37.5)	
Primary diagnosis, diabetes	11 (25.6)	10 (28.6)	1 (12.5)	0.66
Creatinine at transplant, median (IQR)	6.8 (4.6, 9.2)	7.9 (4.6, 9.2)	6.2 (4.6, 10.3)	0.91
Creatinine at discharge, median (IQR)	1.5 (1.1, 3.8)	1.4 (1.1, 3.8)	1.8 (1.1, 3.7)	0.67
cPRA at transplant (%), median (IQR)	24.0 (0.0, 68.0)	7.5 (0.0, 59.0)	85.5 (12.0, 98.0)	0.04
cPRA at transplant ≥20%, median (IQR)	22 (52.4)	16 (47.1)	6 (75.0)	0.24
On dialysis, pretransplant, *n* (%)	26 (61.9)	21 (61.8)	5 (62.5)	1.00
Yr on dialysis, pretransplant, *n* (%)	3.3 (3.1, 5.3)	3.2 (3.1, 4.4)	4.4 (3.3, 5.3)	0.54
Viral infection at transplant (may have more than one), n (%)				
HBV core antibody (+)	8 (19.0)	6 (17.6)	2 (25.0)	0.64
HbsAg (+)	0 (0.0)	0 (0.0)	0 (0.0)	–
HCV serostatus (+)	5 (11.6)	4 (11.4)	1 (12.5)	1.00
CMV status (+)	37 (86.0)	29 (82.9)	8 (100.0)	0.57
EBV serostatus (+)	39 (97.5)	32 (100.0)	7 (87.5)	0.20
HIV serostatus (+)	0 (0.0)	0 (0.0)	0 (0.0)	–
Any viral infection at transplant	43 (100.0)	35 (100.0)	8 (100.0)	–
Kidney transplant procedure type				0.53
Left	26 (63.4)	22 (66.7)	4 (50.0)	
Right	14 (34.1)	10 (30.3)	4 (50.0)	
En-bloc	1 (2.4)	1 (3.0)	0 (0.0)	
HLA mismatch level, median (IQR)	4.5 (3.0, 5.0)	5.0 (4.0, 5.0)	3.5 (2.0, 5.0)	0.23
HLA mismatch level ≥5, median (IQR)	21 (50.0)	18 (52.9)	3 (37.5)	0.70
Glomerular sclerosis at transplant (%), median (IQR)	1.3 (0.0, 5.8)	1.4 (0.0, 5.8)	0.6 (0.0, 4.3)	0.68
Number of glomerular sclerosis at transplant, median (IQR)	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.5 (0.0, 2.0)	0.71
Interstitial fibrosis at transplant, *n* (%)				1.00
0%–5%	36 (83.7)	29 (82.9)	7 (87.5)	
6%–25%	6 (14.0)	5 (14.3)	1 (12.5)	
26%–50%	1 (2.3)	1 (2.9)	0 (0.0)	
Tubular atrophy at transplant, *n* (%)				1.00
None	29 (67.4)	23 (65.7)	6 (75.0)	
1%–25%	14 (32.6)	12 (34.3)	2 (25.0)	
Tubular atrophy at transplant, *n* (%)				1.00
≤11%	41 (95.3)	33 (94.3)	8 (100.0)	
>11%	2 (4.7)	2 (5.7)	0 (0.0)	
Arterial fibrosis at transplant, *n* (%)				1.00
None	35 (81.4)	28 (80.0)	7 (87.5)	
1%–25%	7 (16.3)	6 (17.1)	1 (12.5)	
26%–50%	1 (2.3)	1 (2.9)	0 (0.0)	

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Table 1. (Continued) Correlation of donor and recipient characteristics with graft failure recipient and donor characteristics in MTP cohort, by composite event of death-censored graft failure or eGFR <30 ml/min per 1.73 m^2

	1.1. Composite event (of death-censored graft failure)			
Demographic and clinical characteristics	**Total (N = 43)**	**No event (n = 35)**	**Event (n = 8)**	***P*-value**
Arterial fibrosis at transplant, *n* (%)				1.00
≤11%	42 (97.7)	34 (97.1)	8 (100.0)	
>11%	1 (2.3)	1 (2.9)	0 (0.0)	
Glomerular thrombi at transplant (%), median (IQR)	6.6 (3.3, 16.6)	6.3 (3.1, 13.3)	13.9 (6.6, 21.6)	0.14
Arterial/arteriolar thrombi at transplant, *n* (%)				1.00
Absent	36 (83.7)	29 (82.9)	7 (87.5)	
Present	7 (16.3)	6 (17.1)	1 (12.5)	
Thrombi in cortical/medullary capillary at transplant, *n* (%)				1.00
Absent	42 (97.7)	34 (97.1)	8 (100.0)	
Present	1 (2.3)	1 (2.9)	0 (0.0)	
Donor characteristics				
Donor age (yr), median (IQR)	39.0 (28.0, 48.0)	38.0 (28.0, 48.0)	47.5 (31.5, 50.0)	0.40
Donor male gender, *n* (%)	24 (55.8)	18 (51.4)	6 (75.0)	0.27
Donor race/ethnicity, *n* (%)				0.40
White	22 (51.2)	17 (48.6)	5 (62.5)	
Black	4 (9.3)	3 (8.6)	1 (12.5)	
Hispanic/Latino	14 (32.6)	13 (37.1)	1 (12.5)	
Asian	2 (4.7)	1 (2.9)	1 (12.5)	
Other	1 (2.3)	1 (2.9)	0 (0.0)	
Donor BMI, median (IQR)	25.1 (22.5, 28.1)	24.6 (22.5, 29.0)	25.3 (24.7, 26.2)	0.78
Kidney cold ischemic time (h), median (IQR)	12.9 (1.1, 22.2)	12.0 (1.0, 18.3)	22.5 (7.0, 32.8)	0.09
Donor history of smoking, *n* (%)	7 (16.3)	5 (14.3)	2 (25.0)	0.60
Donor history of hypertension, *n* (%)	9 (21.4)	7 (20.6)	2 (25.0)	1.00
Donor history of diabetes, *n* (%)	1 (3.6)	1 (4.5)	0 (0.0)	1.00
Donor viral infection at transplant (may have more than one), *n* (%)				
HBV core antibody (+)	0 (0.0)	0 (0.0)	0 (0.0)	–
CMV status (+)	22 (64.7)	18 (64.3)	4 (66.7)	1.00
EBV serostatus (+)	13 (86.7)	11 (84.6)	2 (100.0)	1.00
HIV serostatus (+)	0 (0.0)	0 (0.0)	0 (0.0)	–
Any viral infection at transplant	33 (76.7)	27 (77.1)	6 (75.0)	1.00
Donor type, *n* (%)				0.69
Living	15 (34.9)	13 (37.1)	2 (25.0)	
Deceased	28 (65.1)	22 (62.9)	6 (75.0)	
Donor type, *n* (%)				0.83
Living	15 (34.9)	13 (37.1)	2 (25.0)	
Donation after brain-stem death (DBD)	25 (58.1)	19 (54.3)	6 (75.0)	
Donation after circulatory death (DCD)	3 (7.0)	3 (8.6)	0 (0.0)	
Deceased donor type				1.00
Donation after circulatory death (DCD)	3 (10.7)	3 (13.6)	0 (0.0)	
Donation after brain-stem death (DBD)	25 (89.3)	19 (86.4)	6 (100.0)	
Pump perfusion (vs. Ice), *n* (%)				0.27
On ice	19 (44.2)	17 (48.6)	2 (25.0)	
Pump	24 (55.8)	18 (51.4)	6 (75.0)	
Outcomes				
Follow-up time (yr), median (IQR)	6.8 (5.0, 8.8)	6.8 (5.0, 9.9)	6.7 (5.0, 7.5)	0.62
All-cause mortality, *n* (%)	12 (27.9)	10 (28.6)	2 (25.0)	1.00
Grafts with > 20% glomeruli showing thrombi in postperfusion biopsy, *n* (%)	8 (18.6)	6 (17.1)	2 (25.0)	0.63
Tubular brush border cells in glomeruli, *n* (%)	3 (7.0)	3 (8.6)	0 (0.0)	1.00
Vascular pole showing thrombi, *n* (%)	1 (2.3)	1 (2.9)	0 (0.0)	1.00
Platelet IHC stain, *n* (%)	1 (2.3)	0 (0.0)	1 (12.5)	0.19
Last eGFR in follow-up (ml/min per 1.73 m^2), *n* (%)				<0.001
≥60	19 (45.2)	18 (52.9)	1 (12.5)	
30–60	17 (40.5)	16 (47.1)	1 (12.5)	
<30	6 (14.3)	0 (0.0)	6 (75.0)	
Graft loss (not death-censored), *n* (%)	14 (32.6)	10 (28.6)	4 (50.0)	0.40
Graft loss (death-censored), *n* (%)	2 (4.7)	0 (0.0)	2 (25.0)	0.03
Graft failure (death-censored graft loss or last eGFR <30), *n* (%)	–	–	–	–

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Table 1. (Continued) Correlation of donor and recipient characteristics with graft failure recipient and donor characteristics in MTP cohort, by composite event of death-censored graft failure or eGFR <30 ml/min per 1.73 m^2

	1.1. Composite event (of death-censored graft failure)			
Demographic and clinical characteristics	**Total (N = 43)**	**No event (n = 35)**	**Event (n = 8)**	***P*-value**
Last eGFR in follow-up (ml/min per 1.73 m^2), median (IQR)	58.0 (43.0, 75.0)	62.0 (52.0, 83.0)	27.0 (24.0, 40.0)	<0.001
Last eGFR in follow-up <30 (ml/min per 1.73 m^2), *n* (%)	6 (14.0)	0 (0.0)	6 (75.0)	<0.001
Last eGFR in follow-up <60 (ml/min per 1.73 m^2), *n* (%)	23 (53.5)	16 (45.7)	7 (87.5)	0.051
Repeat transplant biopsy with TMA, *n* (%)	1 (2.3)	0 (0.0)	1 (12.5)	0.19
Repeat biopsy showing progressive scarring >10% in cortical compartments in subsequent biopsies, *n* (%)				0.14
No	16 (69.6)	13 (81.3)	3 (42.9)	
Yes	7 (30.4)	3 (18.8)	4 (57.1)	
Delayed graft function present, *n* (%)	13 (30.2)	9 (25.7)	4 (50.0)	0.22
Post-transplant proteinuria, present, *n* (%)	15 (36.6)	9 (27.3)	6 (75.0)	0.04
Post-transplant proteinuria ≥2+, *n* (%)	13 (32.5)	7 (21.9)	6 (75.0)	0.01
Rejection episodes present, *n* (%)	3 (7.0)	1 (2.9)	2 (25.0)	0.08
Grafts with thrombi				0.18
Thrombi ≤20%	35 (89.7)	29 (93.5)	6 (75.0)	
Thrombi >20% + scaring ≤10%	0 (0.0)	0 (0.0)	0 (0.0)	
Thrombi >20% + scaring >10%	4 (10.3)	2 (6.5)	2 (25.0)	
Grafts with thrombi				0.30
Thrombi ≤20%	35 (81.4)	29 (82.9)	6 (75.0)	
Thrombi >20% + no DGF	3 (7.0)	3 (8.6)	0 (0.0)	
Thrombi >20% + DGF	5 (11.6)	3 (8.6)	2 (25.0)	
Grafts with thrombi				0.39
Thrombi ≤20%	35 (81.4)	29 (82.9)	6 (75.0)	
Thrombi >20% + living donor	2 (4.7)	1 (2.9)	1 (12.5)	
Thrombi >20% + deceased donor	6 (14.0)	5 (14.3)	1 (12.5)	
In patients with grafts with > 20% glomeruli showing thrombi				0.61
Thrombi ≤20%	35 (81.4)	29 (82.9)	6 (75.0)	
Thrombi >20% + living donor	2 (4.7)	1 (2.9)	1 (12.5)	
Thrombi >20% + DBD	5 (11.6)	4 (11.4)	1 (12.5)	
Thrombi >20% + DCD	1 (2.3)	1 (2.9)	0 (0.0)	

BMI, body mass index; cPRA, calculated panel-reactive antibody; eGFR, estimated glomerular filtration rate; HLA, human leukocyte antigen; IQR, interquartile range.

significant association with acute rejection episodes (*P*-value 0.03) (Supplementary Table S3).

In the propensity score-matched cohorts, patients with MTP appeared to have a high risk of graft failure compared with non-MTP patients; however, the difference was not statistically significant (Hazard ratio 1.73; 95% confidence interval 0.56, 5.29; $P = 0.34$). (Supplementary Figure S1)

In the MTP group, presence of calculated panel-reactive antibody (cPRA) at transplantation was significantly associated with death-censored graft failure as well as a persistent estimated glomerular filtration rate <30 ml/min per 1.73m^2 ($P = 0.04$ and 0.01, respectively) (Table 1, Supplementary Figure S2)

The presence of proteinuria of >2+ by dipstick during the posttransplant period was significantly associated with death-censored graft failure ($P = 0.01$) in patients with MTP and the statistical significance was consistent for any level of posttransplant urine protein ($P = 0.04$) (Supplementary Figures S3 and S4)

However, there was no statistically significant association between the presence or quantity of cPRA between the MTP group and biopsies without thrombi.

MTP, irrespective of the quantity, was not associated with the death-censored graft failure (Supplementary Figure S5). Although diffuse microthrombi were significantly associated with progressive renal cortical scarring ($P = 0.004$, Supplementary Table S4), diffuse microthrombi did not show a significant association with graft failure in overall as well as with matched controls (Supplementary Table S4, and Supplementary Figures S6 and S7)

DISCUSSION

Most significantly, our findings document that microthrombi, if present diffusely, are associated with progressive renal scarring in long-term follow-up on repeat biopsies. Also, the presence of significant proteinuria and cPRA, in the MTP group were associated with graft loss. Our study documents one of the largest series of MTP with meticulous histo-pathological analysis and long-term follow-up. Graft outcome analysis is limited by smaller numbers and confounding graft injury due to several causes.

Our findings of rapid resolution of MTP in repeat biopsies was consistent with previous reports.[2–4] Our study voices a novel caution in the differential diagnosis of microthrombi. We noted that fragmented proximal tubular cells somehow entrapped in the glomerular capillary lumen may closely simulate microthrombi in routine light microscopy (Figure 1). These renal tubular fragments can definitively be identified with immunohistochemistry, by the absence of CD61a, and the presence of PAX8 and CD10, nuclear and cytoplasmic markers, respectively, for tubular cell nuclei and brush border respectively. It is pertinent to note that grafts from donors with severe disseminated intravascular coagulation and renal dysfunction showed normal biopsies 3 months posttransplant.[5]

We found a statistically significant association of graft failure with presence of cPRA in the MTP patients. This important association has not been reported, and this finding may suggest a possible transient immune-mediated insult in the pathogenesis of this condition. There are independent reports of cPRA at transplantation on poorer graft outcome.[6–8]

However, diffuse microthrombi impart a significant risk of progressive renal scarring. The presence of microthrombi is also a risk factor for subsequent development of proteinuria, which is an independent risk for graft failure.[9]

Though MTP was a transient pathology, which spontaneously resolves, it is potentially associated with significant endothelial damage and ensuing progressive increase in glomerular sclerosis and interstitial fibrosis or tubular atrophy. We found that the presence of microthrombi, regardless of its extent, has no independent statistical association with graft failure, in line with previous studies.[1–4]

DISCLOSURE

All the authors declared no competing interest.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Supplementary Methods.

Figure S1. Kaplan Meier survival curves for freedom from composite event by MTP status.

Figure S2. cPRA at transplant (%) by graft failure status.

Figure S3. Freedom from composite event of death-censored graft loss for any proteinuria.

Figure S4. Freedom from composite event of death-censored graft loss for proteinuria >2+.

Figure S5. Freedom from composite event of death-censored graft loss for diffuse thrombi.

Figure S6. Freedom from composite event of death-censored graft loss for progressive cortical scarring.

Figure S7. Freedom from composite event of death-censored graft loss for MTP compared to non-MTP group.

Table S1. Recipient and donor characteristics in study and control group.

Table S2. Recipient and donor characteristics in study and propensity-matched cohort group.

Table S3. Univariable Cox regression for composite event of death-censored graft failure or eGFR <30 ml/min per 1.73 m^2.

Table S4. Progressive scarring, proteinuria and cPRA with >20% glomeruli with thrombi.

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