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Transplant nephrectomy; pathological features of 124 consecutive cases in a single center study over 10 years

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ABSTRACT

Background: Transplant nephrectomy (TN) is not commonly performed but it may be essential for several indications.

Objectives: This study details an in-depth evaluation of the histological changes present in TN specimens.

Patients and Methods: We identified 124 consecutive TN cases between 2004 and 2014. The indication for TN was divided into four groups: acute graft loss without significant blood flow (AGL group- 47 cases); suspected ongoing rejection or graft intolerance syndrome (Rej/GIS group- 44 cases); infection (INF group- 24 cases); and miscellaneous reasons (MIS group- 9 cases). We examined the histological changes, including the main renal artery (MRA), intrarenal arteries, the renal vein and the ureter.

Results: In AGL group, most cases showed no tubulointerstitial inflammation, interstitial fibrosis and tubular atrophy, but 74.5% had necrosis. All cases in Rej/GIS group showed severe interstitial fibrosis and tubular atrophy, since 40.9% showed severe tubulointerstitial inflammation. Glomerulitis was observed in 52.3% and transplant glomerulopathy (TG) was detected in 75.0%. Arteritis of intrarenal arteries and the MRA were detected in 70.5% and 59.1%. In INF group, 66.7% had tubulitis and 79.2% had interstitial inflammation with lymphocytes, and severe interstitial fibrosis while, tubular atrophy were detected in 66.7%. TG was detected in 62.5%. In MIS group, the histological changes were minor.

Conclusions: This study provides a detailed description of the morphological characteristics associated with various indications for TN. TN will occasionally reveal unexpected and significant findings that may require specific forms of treatment to manage the patient appropriately.

Implication for health policy/practice/research/medical education:
Transplant nephrectomy is not commonly performed but it may be essential for several indications. The histological changes of failed grafts are similar and often specific between each indication.

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Original Article

1. Background

Transplant nephrectomy (TN) is infrequently required for various reasons at any period post-transplant. The indication for TN depends on the patient's medical condition and each unit's local policy as there are no standard National or International guidelines. A variety of indications for TN are reported (1-9), and these are mostly divided into immunological and non-immunological. Uncontrollable rejection is the most common immunological indication for TN. With non-immunological reasons, a necrotic graft following graft failure requires urgent removal. Refractory infection may also require TN to allow withdrawal of immunosuppression.

Nephrectomised grafts might be expected to show

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a range of predictable morphological findings, but it is important that unexpected findings that may impact on future management are not overlooked. However, detailed histological features of graft nephrectomy have not previously been described in detail, while, there is very little published literature outlining the histological findings of graft nephrectomy specimens (10-12). In addition, histopathological changes of the large vessels and ureter specifically have not been reported on at all.

2. Objectives

This study was performed to review and document the pathological findings of 124 TN specimens. After allocating them to four groups according to the indication for TN, we examined the acute and chronic changes and also looked at the renal artery, renal vein and ureter. Analysis of the histological changes in a nephrectomised graft may help to understand immunological and non-immunological damage to the graft before TN.

3. Patients and Methods

3.1. Patients and indications for TN

One hundred-twenty-four consecutive TN cases were enrolled in this study. All cases were performed at the Royal London Hospital over a 10-year period from December 2004 to December 2014. One hundred and six original transplants had been performed at our hospital and the remaining 18 transplants were done at various other hospitals, with follow up at our hospital. The age of the recipient at the time of transplantation was 37.6±14.3 years old. There were 79 male and 45 female patients. Ninety-three allografts were provided by deceased donors and the other 31 allografts were from living donors. The majority were primary transplants (n=99) and the remaining were sequential transplants (n=25). The overall interval from transplantation to graft loss, from graft loss to TN, and from transplantation to TN, was 10.0 (interquartile range, IQR: 0.2-65.0), 1.7 (IQR: 0-8.7) and 16.0 (IQR: 0.5-71.4) months.

The indications of all TNs were divided into four main groups; acute graft loss (AGL group), suspected on-going acute rejection and/or graft intolerance syndrome (Rej/GIS group), infection (INF group), and miscellaneous reasons (MIS group). AGL was defined as insignificant blood flow due to a circulatory disorder or vascular complication. Rej/GIS showed symptoms including tenderness around graft, hematuria or fever without infection. Some cases in this group also had abnormal biochemical laboratory data such as hypoalbuminemia, erythropoietin resistant anemia, and elevated C-reactive protein. Rej/GIS group underwent TN in order to remove a graft which was believed to be the cause of these symptoms. The INF group required TN and withdrawal of immunosuppressive agents because of refractory bacterial, viral or fungal infection diagnosed by positive culture and/or positive serology. Locally infected grafts and systemic infections were both included in the INF group. TN in the INF group was required for the purpose of resolving persistent infection and stopping immunosuppression. MIS was defined as TN for reasons not applicable to the other three groups.

3.2. Histopathological assessment

Resected graft specimens were routinely assessed by the pathology department at the Royal London Hospital. All specimens were formalin fixed and sampled to produce blocks of parenchyma and vasculature. Haematoxylin-eosin, periodic acid-Schiff, hexamine sliver and C4d were performed in all cases. Morphological changes were evaluated in the graft parenchyma, the renal artery, the renal vein and the ureter. At least three sections were available from the renal parenchyma in all cases. The specimens were scored by three individuals (MM, MS and AL) using recognized criteria according to the Banff classification (13). In each case the main renal artery (MRA), the intrarenal arteries (IAs) and renal vein were specifically examined for the formation of thrombosis. Histological changes in MRA were scored in a similar way as a described intrarenal artery in the Banff classification. The presence of venous endothelialitis was also examined, and the ureter was examined for inflammation and necrosis. In addition, the type of infiltrating cell (lymphocyte, plasma cell, neutrophil and eosinophil) was noted in all inflammatory lesions.

3.3. Ethical approval

This study was undertaken as part of a clinical improvement project and was granted ethical approval by clinical governance team application (ID number 9958). The research followed the tenets of the Declaration of Helsinki.

3.4. Statistical analysis

All values are shown mean and standard deviation, median (IQR), or percentage. Continuous variables were compared using the student *t* test or Steel-Dwass test, and categorical variables were analysed using the Chi-square or Fisher's exact test. The differences were considered statistically significant at $P<0.05$. JMP version 12 software (SAS Institute Inc, Cary, NC, USA) was used for all statistical analyses.

4. Results

4.1. Indication and timing of TN

Forty-seven patients (37.9%) received TN for AGL and it was the commonest reason for TN (Table 1). All cases in the AGL group underwent TN within 6 months post-

Table 1. Reasons of transplant nephrectomy

	No. (%)
AGL (n=47)	
a) Acute circulatory disorder	
Venous thrombosis	18 (14.5)
Arterial thrombosis	10 (8.1)
Primary non-function	9 (7.3)
Hemolytic uremic syndrome	3 (2.4)
b) Bleeding	4 (3.2)
c) Technical complication	3 (2.4)
Rej/GIS (n=44)	44 (35.5)
INF (n=24)	
Urinary tract infection	17 (13.7)
Hepatitis C	2 (1.6)
CMV infection	1 (0.8)
BK virus infection	1 (0.8)
Pulmonary tuberculosis	1 (0.8)
Infected lymphocele	1 (0.8)
Sepsis	1 (0.8)
MIS (n=9)	
Preparation for subsequent transplantation	4 (3.2)
Recipient malignancy	3 (2.4)
Donor malignancy	1 (0.8)
Recurrent FSGS	1 (0.8)

AGL, acute graft loss; Rej/GIS, suspected ongoing rejection/graft intolerance syndrome; INF, infection; CMV, cytomegalovirus; MIS, miscellaneous; FSGS, focal segmental glomerulosclerosis.

transplant. The AGL group had three main reasons for TN; acute circulatory disorder, bleeding and technical complication. Acute circulatory disorder was further subdivided into venous thrombosis, arterial thrombosis, primary non-function, and thrombotic microangiopathy. In the TNs due to Rej/GIS, the second commonest indication (n=44, 35.5%), all cases required TN after returning to dialysis. In the TNs due to INF, urinary tract infection was common. Of 24 cases in INF group, 6 still had a degree of graft function but 18 required dialysis. The MIS group comprised 9 cases (7.3%) and 4 cases underwent TN purely in preparation for a subsequent transplant. One case needed to have immediate TN after detection of gall bladder cancer in the deceased donor. Other reasons included management of Kaposi sarcoma, the development of post-transplant lymphoproliferative disorders and a renal mass lesion. All needed removal of the graft to discontinue immunosuppression. The time from transplantation to graft loss in AGL group was significantly shorter than the other three groups (AGL 0.13 month vs Rej/GIS 39.9 months; INF 61.0 months; MIS 127.0 months, $P<0.001$) (Table 2). AGL and MIS groups had very early TN after graft loss while Rej/GIS showed the longest interval between graft loss and TN (8.9 months).

4.2 Histological findings according to the indication for TN

4.2.1. AGL group

AGL group was less likely to have tubulointerstitial morphological changes compared with the other three groups, but 74.5% had some necrosis in the background (Tables 3 and 4). The tubules and interstitium were mostly normal - t0 and i0 was found shown in 39 cases (83.0%) and 37 cases (78.7%) respectively. t3 and i3 were detected in only 3 cases (6.4%) and 1 case (2.1%). Where present, lymphocytes were the dominant type of inflammatory cell in the interstitium. Chronic changes were also unusual, and ct0 and ci0 were common (83.0% and 80.9%). Severe tubular atrophy (ct3) and severe interstitial fibrosis (ci3) was found in only 3 cases (6.4%). Glomeruli were more frequently normal than in the other three groups. Glomerulitis was absent in most cases (89.4%). Transplant glomerulopathy (TG) and mesangial matrix increase was not observed in 83.0% and 68.1%, while g3 and cg3 was not seen at all. There was very little global glomerulosclerosis (GS) and no cases showed over 25% GS. MRAs and IAs showed arteritis in 38.3% and 25.5% cases (Table 4). Of note, neutrophil rich arteritis was observed in 29.8% of MRAs and 19.2% of IAs. The renal vein had less acute inflammation than the arteries, but thrombus formation was found in 29 cases (61.7%). Intimal thickening of MRAs and IAs was found in 68.1% and 76.6%, respectively. However, these rates in AGL group were lower than those in the other three groups. In particular, cv3 was observed in only 3 cases (6.4%). 63.8% had also no arteriolar hyalinosis whilst ah2-3 was present in 23.4%. C4d expression was detected in only 3 cases. In the ureter, necrosis and inflammation was detected in 52.6% and 55.3%. Plasma cells and eosinophils were uncommonly found in the ureter (Table 5).

Table 2. Timing of transplant nephrectomy

	AGL (n=47)	Rej/GIS (n=44)	INF (n=24)	MIS (n=9)
Time from transplantation to graft loss (mon)	0.13 (0-0.57)[a,b,c]	39.9 (14.5-157.4)[a]	61.0 (10.5-148.4)[b]	127 (14.6-220.7)[c]
Interval from graft loss to transplant nephrectomy (mon)	0.0 (0.0-0.2)[d,e]	8.9 (3.4-17.6)[d,f]	3.7 (0-19.1)[e]	0.0 (0.0-1.2)[f]

Data are median (IQR), significance: [a-e] $P<0.001$

AGL, acute graft loss; Rej/GIS, suspected ongoing rejection/graft intolerance syndrome; INF, infection; MIS, miscellaneous.

Table 3. Histological findings and distribution of inflammatory cell (tubules, interstitium and glomerulus)

	All (n=124)	AGL (n=47)	Rej/GIS (n=44)	INF (n=24)	MIS (n=9)	*P*
Tubules						
Tubulitis						
t0	53 (42.7%)	39 (83.0%)	2 (4.6%)	7 (29.2%)	5 (55.6%)	
t1	13 (10.5%)	3 (6.4%)	5 (11.4%)	3 (12.5%)	2 (22.2%)	
t2	25 (20.2%)	2 (4.3%)	15 (34.1%)	6 (25.0%)	2 (22.2%)	
t3	28 (22.6%)	3 (6.4%)	18 (40.9%)	7 (29.2%)	0	
NA	5 (4.0%)	0	4 (9.1%)	1 (4.2%)	0	
Tubular atrophy						
ct0	41 (33.1%)	39 (83.0%)	0	1 (4.2%)	1 (11.1%)	
ct1	5 (4.0%)	3 (6.4%)	0	1 (4.2%)	1 (11.1%)	
ct2	12 (9.7%)	2 (4.3%)	0	6 (25.0%)	4 (44.4%)	
ct3	66 (53.2%)	3 (6.4%)	44 (100%)	16 (66.7%)	3 (33.3%)	
Interstitium						
Interstitial inflammation						
i0	48 (38.7%)	37 (78.7%)	2 (4.6%)	5 (20.8%)	4 (44.4%)	
i1	21 (16.9%)	6 (12.8%)	7 (15.9%)	4 (16.7%)	4 (44.4%)	
i2	25 (20.2%)	3 (6.4%)	17 (38.6%)	4 (16.7%)	1 (11.1%)	
i3	30 (24.2%)	1 (2.1%)	18 (40.9%)	11 (45.8%)	0	
Type of infiltrating cell (i)						
Lymphocyte	76 (61.3%)	10 (21.3%)	42 (95.5%)	19 (79.2%)	5 (55.6%)	<0.001
Plasma cell	37 (29.8%)	1 (2.1%)	30 (68.2%)	6 (25.0%)	0	<0.001
Neutrophil	13 (10.5%)	3 (6.4%)	7 (15.9%)	3 (12.5%)	0	0.337
Eosinophil	17 (13.7%)	0	13 (29.5%)	3 (12.5%)	1 (11.1%)	<0.001
ci0	40 (32.3%)	38 (80.9%)	0	1 (4.2%)	1 (11.1%)	
ci1	6 (4.8%)	4 (8.5%)	0	1 (4.2%)	1 (11.1%)	
ci2	12 (9.7%)	2 (4.3%)	0	6 (25.0%)	4 (44.4%)	
ci3	66 (53.2%)	3 (6.4%)	44 (100%)	16 (66.7%)	3 (33.3%)	
Glomerulus						
Glomerulitis						
g0	85 (68.6%)	42 (89.4%)	18 (40.9%)	16 (66.7%)	9 (100%)	
g1	16 (12.9%)	3 (6.4%)	9 (20.5%)	4 (16.7%)	0	
g2	14 (11.3%)	2 (4.3%)	10 (22.7%)	2 (8.3%)	0	
g3	5 (4.0%)	0	4 (9.1%)	1 (4.2%)	0	
NA	4 (3.2%)	0	3 (6.8%)	1 (4.2%)	0	
Transplant glomerulopathy						
cg0	60 (48.4%)	39 (83.0%)	8 (18.2%)	8 (33.3%)	5 (55.6%)	
cg1	25 (20.2%)	5 (10.6%)	11 (25.0%)	7 (29.2%)	2 (22.2%)	
cg2	19 (15.3%)	3 (6.4%)	9 (20.5%)	5 (20.8%)	2 (22.2%)	
cg3	16 (12.9%)	0	13 (29.5%)	3 (12.5%)	0	
NA	4 (3.2%)	0	3 (6.8%)	1 (4.2%)	0	
Mesangial matrix increase						
mm0	51 (41.1%)	32 (68.1%)	11 (25.0%)	5 (20.8%)	3 (33.3%)	
mm1	31 (25.0%)	11 (23.4%)	11 (25.0%)	7 (29.2%)	2 (22.2%)	
mm2	29 (23.4%)	3 (6.4%)	13 (29.5%)	9 (37.5%)	4 (44.4%)	
mm3	9 (7.3%)	1 (2.1%)	6 (13.6%)	2 (8.3%)	0	
NA	4 (3.2%)	0	3 (6.8%)	1 (4.2%)	0	
Glomerular sclerosis						
GS <5%	46 (37.1%)	42 (89.4%)	0	3 (12.5%)	1 (11.1%)	
GS 5-25%	16 (12.9%)	5 (10.6%)	4 (9.1%)	4 (16.7%)	2 (22.2%)	
GS 25-50%	9 (7.3%)	0	3 (6.8%)	4 (16.7%)	2 (22.2%)	
GS 50-75%	10 (8.1%)	0	6 (13.6%)	2 (8.3%)	2 (22.2%)	
GS >75%	43 (34.7%)	0	31 (70.5%)	10 (41.8%)	2 (22.2%)	

AGL, acute graft loss; Rej/GIS, suspected ongoing rejection/graft intolerance syndrome; INF, infection; MIS, miscellaneous; NA, not available; GS, glomerular sclerosis.

Table 4. Histological findings and distribution of inflammatory cell (vessels)

	All (n=124)	AGL (n=47)	Rej/GIS (n=44)	INF (n=24)	MIS (n=9)	*P*
Vasculitis						
MRA						
MRA-v0	74 (59.7%)	29 (61.7%)	18 (40.9%)	18 (75.0%)	9 (100%)	
MRA-v1	31 (25.0%)	15 (31.9%)	12 (27.3%)	4 (16.7%)	0	
MRA-v2	11 (8.9%)	2 (4.3%)	8 (18.2%)	1 (4.2%)	0	
MRA-v3	8 (6.5%)	1 (2.1%)	6 (13.6%)	1 (4.2%)	0	
Type of infiltrating cell (MRA)						
Lymphocyte	36 (29.2%)	4 (8.5%)	26 (59.1%)	6 (25.0%)	0	<0.001
Plasma cell	8 (6.5%)	1 (2.1%)	6 (13.6%)	1 (4.2%)	0	0.109
Neutrophil	21 (16.9%)	14 (29.8%)	6 (13.6%)	1 (4.2%)	0	0.015
Eosinophil	3 (2.4%)	0	3 (6.8%)	0	0	0.133
IAs						
v0	75 (60.5%)	35 (74.5%)	13 (29.5%)	18 (75.0%)	9 (100%)	
v1	21 (16.9%)	8 (17.0%)	10 (22.7%)	3 (12.5%)	0	
v2	15 (12.1%)	3 (6.4%)	9 (20.5%)	3 (12.5%)	0	
v3	13 (10.5%)	1 (2.1%)	12 (27.3%)	0	0	
Type of infiltrating cell (IAs)						
Lymphocyte	41 (33.1%)	5 (10.6%)	30 (68.2%)	6 (25.0%)	0	<0.001
Plasma cell	7 (5.7%)	1 (2.1%)	6 (13.6%)	0	0	0.040
Neutrophil	22 (17.7%)	9 (19.2%)	12 (27.3%)	1 (4.2%)	0	0.051
Eosinophil	9 (7.3%)	0	8 (18.2%)	1 (4.2%)	0	0.006
Vein						
Venulitis	20 (16.1%)	7 (14.9%)	10 (22.7%)	3 (12.5%)	0	
Type of infiltrating cell (venulitis)						
Lymphocyte	14 (11.3%)	4 (8.5%)	7 (15.9%)	3 (12.5%)	0	0.479
Plasma cell	7 (5.7%)	0	6 (13.6%)	1 (4.2%)	0	0.033
Neutrophil	14 (11.3%)	6 (12.8%)	7 (15.9%)	1 (4.2%)	0	0.334
Eosinophil	5 (4.0%)	0	5 (11.4%)	0	0	0.024
Intimal thickening						
MRA						
MRA-cv0	16 (12.9%)	15 (31.9%)	0	0	1 (11.1%)	
MRA-cv1	41 (33.1%)	24 (51.1%)	8 (18.2%)	5 (20.8%)	4 (44.4%)	
MRA-cv2	29 (23.4%)	5 (10.6%)	13 (29.5%)	11 (45.8%)	0	
MRA-cv3	38 (30.7%)	3 (6.4%)	23 (52.3%)	8 (33.3%)	4 (44.4%)	
IAs						
cv0	13 (10.5%)	11 (23.4%)	1 (2.3%)	0	1 (11.1%)	
cv1	27 (21.8%)	21 (44.7%)	2 (4.6%)	2 (8.3%)	2 (22.2%)	
cv2	28 (22.6%)	12 (25.5%)	8 (18.2%)	6 (25.0%)	2 (22.2%)	
cv3	56 (45.2%)	3 (6.4%)	33 (75.0%)	16 (66.7%)	4 (44.4%)	
Arteriole hyalinosis						
ah0	56 (45.2%)	30 (63.8%)	18 (40.9%)	3 (12.5%)	5 (55.6%)	
ah1	13 (10.5%)	6 (12.8%)	5 (11.4%)	1 (4.2%)	1 (11.1%)	
ah2	15 (12.1%)	7 (14.9%)	4 (9.1%)	4 (16.7%)	0	
ah3	39 (31.5%)	4 (8.5%)	17 (38.6%)	15 (62.5%)	3 (33.3%)	
NA	1 (0.8%)	0	0	1 (4.2%)	0	
C4d positivity	30 (24.2%)	3 (6.4%)	24 (54.5%)	3 (12.5%)	0	<0.001
Formation of thrombosis						
MRA	37 (29.8%)	16 (34.0%)	16 (36.4%)	5 (20.8%)	0	
IAs	20 (16.1%)	8 (17.0%)	11 (25.0%)	1 (4.2%)	0	
Vein	40 (32.3%)	29 (61.7%)	10 (22.7%)	1 (4.2%)	0	
Presence of necrosis	47 (37.9%)	35 (74.5%)	10 (22.7%)	1 (4.2%)	1 (11.1%)	<0.001

AGL, acute graft loss; Rej/GIS, suspected ongoing rejection/graft intolerance syndrome; INF, infection; MIS, miscellaneous; MRA, main renal artery; IAs, intrarenal arteries

Table 5. Ureteral histological findings

	All (n=101)	AGL (n=38)	Rej/GIS (n=33)	INF (n=22)	MIS (n=8)	*P*
Ureteric necrosis	23 (22.8%)	20 (52.6%)	3 (9.1%)	0	0	<0.001
The presence of Inflammation	59 (58.4%)	21 (55.3%)	23 (69.7%)	13 (59.1%)	2 (25.0%)	0.135
Lymphocyte	49 (48.5%)	12 (31.6%)	22 (66.7%)	13 (59.1%)	2 (25.0%)	0.009
Plasma cell	23 (22.8%)	3 (7.9%)	13 (39.4%)	7 (31.8%)	0	0.004
Neutrophil	18 (17.8%)	12 (31.6%)	4 (12.1%)	2 (9.1%)	0	0.036
Eosinophil	15 (14.9%)	0	13 (39.4%)	1 (4.6%)	1 (12.5%)	<0.001

AGL, acute graft loss; Rej/GIS, suspected ongoing rejection/graft intolerance syndrome; INF, infection; MIS, miscellaneous

4.2.2. Rej/GIS group

A variety of tubulointerstitial changes were present in the Rej/GIS group (Table 3). Only 2 cases (4.6%) did not show tubulitis and interstitial inflammation. On the other hand, t3 and i3 was observed in 40.9%. All cases showed ct3 and ci3. The Rej/GIS group tended to have coexistent acute and chronic morphological changes compared with the other three groups (Figure 1). The combination of old and active alterations was also seen in glomerular and vascular lesions. Glomerulitis was detected in 23 cases (52.3%), and 4 cases (9.1%) had g3. TG and mesangial matrix increase was detected in 75.0% and 68.2%. cg3 (29.5%) and mm3 (13.6%) were the highest rates among all groups. The number of cases in the Rej/GIS group increased according to the severity of GS, since, 31 cases (70.5%) had >75% GS. There were high rates of arteritis in IAs and MRAs (70.5% and 59.1%). Remarkably, severe arteritis in IAs and MRAs was present in 12 cases (27.3%) and 6 cases (13.6%). Renal vein showed inflammation in 22.7%. The Rej/GIS group showed a higher rate of venulitis than the other three groups (AGL, INF and MIS: 14.9%, 12.5% and 0%). All but one of the Rej/GIS group had intimal thickening of IAs and MRAs. Severe intimal thickening was commonly found and was present in 52.3% of MRAs and 75.0% of IAs. Around, 40.9% had no arteriolar hyalinosis while ah3 was observed in 38.6%. C4d positivity in the peritubular capillaries was detected in 24 cases (54.5%) and the rate was significantly higher than in the other groups (P<0.001). In terms of ureteric histological changes, necrosis was seen in only 3 cases, while inflammation was present in 23 cases (Table 5). The Rej/GIS group demonstrated various types of infiltrating cells with lymphocytes most commonly found in the interstitium (95.5%), MRA (59.1%), IAs (68.2%) and ureter (66.7%). Moreover, plasma cells and eosinophils seemed to be highly specific for the Rej/GIS group. Plasma cells were found in the interstitial infiltrate in 68.2%, in MRA and IAs walls in 13.6%, in veins in 13.6%, and in the ureter in 39.4%. Eosinophils were observed less frequently than plasma cells, but they were most commonly seen in the Rej/GIS group.

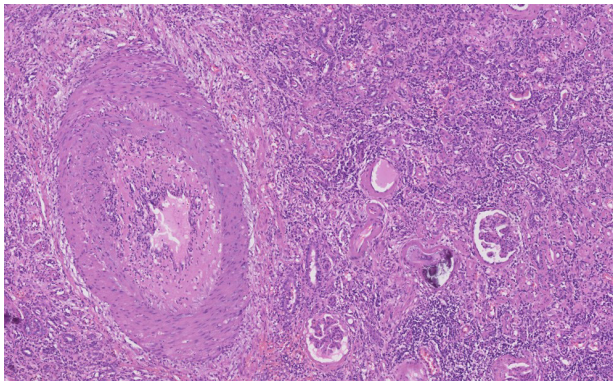

Figure 1. Severe fibrosis with cellular infiltration, severe glomerular sclerosis and moderate arteritis with stenosis.

4.2.3. INF group

The INF group showed less frequent changes than seen in the Rej/GIS group. However, acute tubulointerstitial changes were seen in 66.7% and 79.2% (Table 3). Although t3 was seen in 29.2%, the INF group had the highest rate of i3 (45.8%) among all the groups. Among 23 cases with chronic tubulointerstitial changes, ct3 and ci3 were detected in 16 cases (66.7%). Glomerulitis was observed in 29.2% and was mostly mild (16.7%). On the other hand, TG and mesangial matrix increases were seen in 62.5% and 75.0%. Although MRAs and IAs had intimal thickening, arteritis was seen in only 25%. MRA-cv3 and cv3 were observed in 33.3% and 66.7%, but these grades were mild compared to those in the Rej/GIS group (Table 4). Interestingly, INF frequently showed hyaline arteriolosclerosis with ah score >1 seen in 79.2% and the rate of ah3 (65.2%) was the highest among all groups. C4d expression, vascular thrombosis and necrotic lesion were unusual findings. In INF group, various infiltrating cells were detected in the interstitium and ureter, and lymphocytes were the commonest type of cell (79.2% and 59.1%) (Table5). Plasma cells were also observed in the interstitium and ureter (25.0% and 31.8%), but plasma cells, neutrophils and eosinophils were rarely present in vascular lesions.

4.2.4. MIS group

Nine TNs were performed for clinical need, usually

in asymptomatic patients. As expected, their acute histological changes were minor (Tables 3 and 4). Tubulitis and interstitial inflammation were detected in 4 and 5 cases, but t3, i3, glomerulitis and vasculitis were not observed. In contrast, tubular atrophy, interstitial fibrosis and intimal thickening were present in 88.9%. Expression of C4d and the formation of vascular thrombosis were not observed. Ureteric changes were rare (Table 5). There was no ureteric necrosis, but 2 cases had a degree of ureteric inflammation. In this group, the infiltrating cells were mainly lymphocytes, located in the interstitium and ureter.

4.3 Incidental histological findings

There were unusual, and occasionally unique, histological findings in 6 nephrectomised specimens (4.8%). These included malignancy, infection and metabolic disease. Malignancy was found in 3 cases. One graft, which underwent TN at 10 years 8 months post-transplant, contained a chromophobe neoplasm, 1.1mm in diameter in cortex. Another graft, TN at 16 years 5 months post-transplant, had Type 1 papillary cell tumour which was located peripherally in the cortex, measuring 4 mm in diameter. Post-transplant lymphoproliferative disease related to EB virus was found in a graft resected at 2 years 11 months post-transplant, which was removed because of untreatable BK virus infection. Infection was present in 2 cases. One fungal infection at arterial anastomosis was detected in the AGL group. This case required TN due to a severe uncountable bleeding and hematoma at 24 days post-transplant. There was focal medial necrosis of the renal artery associated with fungal invasion by *Candida*. One case receiving TN for control of pulmonary tuberculosis showed renal tuberculosis with membranous glomerulopathy causing impaired graft function at 3 years post-transplant. There was one case of metabolic disease; AA amyloid was detected in the resected graft after urosepsis at 17 years 9 months post-transplant.

5. Discussion

This study describes the detailed morphological analysis of nephrectomised grafts grouped according to the indication for TN. The histological findings include assessment of the type of infiltrating cells, the vessel changes and alterations of the ureter. All failed grafts seemed to have ongoing immunological and/or non-immunological response irrespective of the indication for TN. Careful pathological attention was paid to whether features might suggest an ongoing response.

In this study, TN due to AGL were mostly unavoidable and surgery was performed urgently to avoid serious later morbidity or mortality. TN due to vascular thrombosis was seen in 22.6% which is higher than previous studies (2.0-24.4%) (1,2,4-8). 35.5% of our cases required TN for on-going suspected acute rejection (AR) and/or graft intolerance syndrome (GIS), although there was no TN due to intractable rejection before graft loss in our study. In contrast, previous reports have suggested that acute and chronic rejection is the most common indication for TN, estimated at 65.3-80.9% and 3.2-57.1% (1-8). Some reports have noted that the incidence of TN due to infection is in the region of 0-3.7% (4-8), which was much lower than our study (19.4%). The indication for TN seems to have changed compared with previous studies and this shift might reflect the current strengthening of immunosuppression, which leads the lower incidence of AR and the higher incidence of infection.

Goral et al analysed histopathological findings of 73 TNs between ≦3 and > 3 months post-transplant (10) and showed that the early TNs had minor changes in acute and chronic histological score. Their results of early TN were similar to our histological findings of AGL group. In the AGL group, acute inflammation following ischemia was the most common morphological change and there was rarely an immunological reaction. These acute inflammatory changes associated with necrosis were neutrophil-dominant; plasma cells and eosinophil were infrequently seen. The cause of the acute circulatory disorder, especially formation of vascular thrombosis, was never clearly established. Therefore, there was always a possibility that vascular damage was related to antibodies mediated injury due to donor specific antibody (DSA). Our study showed that C4d deposition was seen in peritubular capillary in only 2 primary non-function cases and 1 case of renal arterial thrombosis. Of these 3 cases, pre-formed DSA was detected in only one case. C4d detection was absent in 93.6% of the AGL group and it is unlikely that there was involvement of DSA. On the other hand, AGL cases often showed necrosis and this might affect the technical reliability of C4d demonstration. Therefore, antibody mediated rejection might be more common than we were able to demonstrate. Chronic histological lesions in the AGL group were rarely seen because of the shorter duration of graft survival. Remarkably, intimal arterial thickening in this group had a lower rate of score-0 than score-1, and 36.2% had arteriole hyalinosis. These chronic vascular changes are most likely to be of donor origin. Whether these pre-existing vascular changes influenced the possibility of thrombosis is difficult to say.

GIS is reported to represent symptoms considered to be related to chronic inflammation in a failed graft and TN is useful to avoid these symptoms (9,12,14). However, the histological changes of GIS have not been defined. Most Rej/GIS cases with slow progression to graft failure

had tubular atrophy, interstitial fibrosis, TG and chronic vasculopathy, compared with early GL. Various types of infiltrating inflammatory cell were seen in the Rej/GIS group. In particular, plasma cells and eosinophils were commonly seen in this group. These cells reflect cell mediated rejection. Interstitial cellular infiltration by plasma cells and eosinophils is known to occur in AR (15-18). Weir et al described that increased presence of eosinophils in the graft was an adverse prognostic factor for AR (15). Eosinophilic infiltration is also associated with vascular rejection (16). Plasma cell-rich AR occurred at various times post-transplant and it has been related to poorer graft survival (17). Meehan et al reported that late onset plasmacytic AR appears to be poorly responsive to antirejection therapy and portends a poor prognosis for survival of the renal allograft (18). In one study of late AR, C4d positive-acute humoral rejection was often associated with plasma cells (19). Vascular rejection and TG are frequently seen in plasma cell-rich rejection (20). Moreover, plasma cells may be associated with developing chronic rejection (21).

We found that the Rej/GIS group often showed positivity for C4d (54.5%), plasma cells within the interstitium (68.2%) and the presence of vasculitis involving the IAs (70.5%). Our results indicate that the majority of acute histological changes in the Rej/GIS group involved immunological responses for a failed graft. Although a retained non-functioning graft can produce various symptoms, it also has the potential to provoke a severe rejection (10,12). On the other hand, asymptomatic TN nearly always showed an immunological response on histology. We performed TN in asymptomatic patients for 8 cases due to clinical requirements to reduce immunosuppressant in the MIS group. Nevertheless, there were AR grade Ia in 2 cases and borderline changes in 2 cases. Silent non-functioning graft without symptoms can also show AR. Therefore, careful observation for on-going AR should be needed as long as the graft is retained after graft failure.

In the INF group, coexisting acute and chronic morphological changes were seen, as in the Rej/GIS group. In the setting of transplantation, the interpretation of histological changes involving infection is difficult because of the overlapping of immune reaction against graft and organism. The characteristic histological change in the INF group was tubulointerstitial inflammation which was more conspicuous than glomerular and vascular lesions. These histological changes were similar to acute tubulointerstitial nephritis caused after post-transplant urinary tract infection (22). The presence of neutrophils is usually considered to be associated with infection, but it was not specific for the INF group in our study. Although opportunistic infection can develop due to over-immunosuppression, immunosuppressive agents had been reduced in order to control infection much more than routine withdrawal of immunosuppressive agents without infection. This relatively rapid reduction of immunosuppressive agents may simply lead to AR as immunological response before TN. On the other hand, post-transplant infection is reported to activate the immune system leading to AR (23,24). Interestingly, we found arteritis in the INF group only in the presence of urinary tract infection. This may mean that localized bacterial infection activates an immunological response more effectively than systemic infection. Similarly, Audard et al reported a case report in which AR was diagnosed following bacterial pyelonephritis (25).

To our knowledge, there is no detail literature focussing on venulitis and the ureteric changes in TN. The significance of both of these histological changes is unclear and they are not included in the Banff classification. In our study, the venulitis was infrequently found and the changes were not specific for any groups. We revealed that ureteric inflammation was shown in 58.4% of all cases and this rate was relatively high compared with the other inflammatory lesions. Although the resected ureter examined was not always precisely the same portion of ureter in each case, the characteristics of infiltrating cells of the ureter did parallel other lesions. Ureteric histological changes in each group seemed generally to reflect allograft parenchymal alterations.

Incidental histological findings in TN are not frequent, but they are not rare (10). This study found two cases (1.6%) with solid tumour in nephrectomised grafts, but they seemed to be of no clinical significance because of their small size. Generally, incidence of de novo graft carcinomas of the graft is 0.2-1.5% (26,27). Tillou et al found 79 graft carcinomas were detected in over 40 000 transplant recipients (26). In these cases, 6 cases were incidentally diagnosed after TN for chronic rejection of non-functional grafts. Extensive examination of the whole graft is not generally feasible, and it is possible that "tiny" tumours could have been missed.

We have to acknowledge some limitations to our study. DSA was not analysed in this study because the DSA results were not available for all patients. In some cases, the timing of samples for DSA was variable and there was a gap between the sampling and TN. Therefore, the detection of DSA did not always reflect the condition of the patient at the time of TN. We also could not clarify the relationship between C4d staining and DSA regarding antibody mediated rejection. Continuation of immunosuppression after graft loss has advantages and disadvantages (14). The continuation helps to preserve

residual renal function and to prevent AR. On the other hand, it increases the risk of infection, metabolic complication, and cardiovascular complication (28-30). Unfortunately, full data on immunosuppressive status was not available, so it remains uncertain how tapering of immunosuppression influenced the histological changes.

6. Conclusions

In conclusion, this study provides a detailed description of the morphological characteristics associated with various indications for TN. The histological changes are similar and often specific within the TN groups, but different between the groups. Irrespective of whether TN was due to symptoms or not, a substantial and significant immunological and/or non-immunological response appears to be on-going while the graft is retained. Our in-depth histological analysis of failed grafts provides detailed information which may help the development of future guidelines.

Authors' contribution

MM, AA, MY and MS contributed to study design, preparation of manuscript and final revision. YH, AL and CP participated in data gathering. MY and MS conducted data analysis and interpretation. All authors read and approved the paper.

Conflicts of interest

The authors have no sources of funding for this study and have no conflicts of interest to declare.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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