Long-term Trends in the Clinicopathologic Features of Kidney Transplant Recipients With Graft Dysfunction

Yu Ho Lee[a], Jung Jun Lee[b], So-Young Lee[a], Su Woong Jung[c], Yang-Gyun Kim[c], Ju-Young Moon[c], Jin Sug Kim[c], Hyeon Seok Hwang[c], Kyung-Hwan Jeong[c], Byung Ha Chung[d], Chan-Duck Kim[e], Jae Berm Park[f], Yeong Hoon Kim[g], Dong Ho Yang[a], and Sang-Ho Lee[c,*]

[a]Division of Nephrology, Department of Internal Medicine, [b]Department of Surgery, CHA Bundang Medical Center, CHA University, Seongnam, Korea; [c]Division of Nephrology, Department of Internal Medicine, Kyung Hee University, Seoul, Korea; [d]Transplant Research Center, Division of Nephrology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea; [e]Division of Nephrology, Department of Internal Medicine, Kyungpook National University Hospital, Daegu, Korea; [f]Department of Surgery, Samsung Medical Center, Seoul, Korea; and [g]Division of Nephrology, Department of Internal Medicine, Inje University College of Medicine, Busan, Korea

ABSTRACT

Background. Graft biopsy is the gold standard for the differential diagnosis of graft dysfunction. The time interval between transplant surgery and biopsy often provides clinicians with diagnostic clues. However, the clinicopathologic features of late graft biopsy, especially those obtained at more than 5 years after kidney transplant, are not well understood.

Materials and Methods. We retrospectively collected graft biopsy tissues obtained from kidney transplant recipients who underwent indication biopsy between February 2012 and March 2017. Patients were divided according to their post-transplant period, and their clinical characteristics, pathologic diagnosis, and Banff scores were compared across groups.

Results. A total of 410 indication biopsy specimens obtained from 321 kidney transplant recipients were analyzed in this study. Overall, the incidence of T cell–mediated rejection, borderline rejection, and BK virus–associated nephropathy decreased while that of antibody-mediated rejection, nonspecific interstitial fibrosis and tubular atrophy, and glomerulonephritis increased over time. Most samples obtained over 5 years after kidney transplant exhibited chronic glomerular and tubulointerstitial injuries irrespective of their pathologic diagnosis. In patients whose post-transplant period was less than 5 years, urine protein-to-creatinine ratio was significantly elevated in the glomerulonephritis and chronic active antibody-mediated rejection groups only. In contrast, patients who underwent graft biopsy more than 5 years after kidney transplant showed significantly high levels of proteinuria irrespective of the pathologic diagnosis, and there was no statistical difference between groups.

Conclusion. We demonstrated that the etiology of graft dysfunction is largely influenced by the biopsy time point.

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Yu Ho Lee and Jung Jun Lee contributed equally as first authors to this work.

*Address correspondence to Sang-Ho Lee, MD, PhD, Division of Nephrology, Department of Internal Medicine, Kyung Hee University, Seoul, KS013. Tel: +82-2- 440-6121; Fax: +82-2-440-8049. E-mail: lshkidney@khu.ac.kr

230 Park Avenue, New York, NY 10169

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ACUTE allograft dysfunction is one of the most common complications in kidney transplant (KT) recipients that profoundly influences short- and long-term graft outcomes. Currently, graft biopsy is mandatory to distinguish between possible causes of graft dysfunction, such as rejection, infection-related diseases, drug toxicity, and glomerulonephritis. In addition, several studies have demonstrated that biopsy time point after KT may provide important clues for the differential diagnosis of graft dysfunction [1–4]. For example, acute T cell–mediated rejection (TCMR) is the most common cause of transplant functional decline during the first 6 months after KT, after which its incidence declines over time [1,4]. Meanwhile, patients with worsening graft function 1 year post transplant are more likely to show evidence of antibody-mediated rejection (ABMR) [1]. However, most previous studies investigated the chronological trends of diagnosis at no more than 5 years after KT, and data regarding the pathologic features of late graft biopsy, especially those performed at more than 10 years after KT, are lacking. The purpose of this study was to determine the temporal changes in the clinical parameters and pathologic diagnoses among KT recipients.

MATERIALS AND METHODS

Study Design and Patient Recruitment

We retrospectively enrolled KT recipients who underwent indication biopsy in 6 hospitals (Kyung Hee University Hospital at Gangdong, Kyung Hee University Medical Center, Seoul St. Mary's Hospital, Kyungpook National University Hospital, Samsung Medical Center, and Busan-Baik Hospital) between February 2012 and March 2017. Graft biopsy was performed either to evaluate the cause of graft dysfunction, defined as increased serum creatinine levels (25% or more increase in serum creatinine) or persistent proteinuria (1500 mg/gCr or more urine protein-to-creatinine ratio [PCR]) [5,6].

All pathologic diagnoses and scores were determined in accordance with 2007 Banff classification [7]. Calcineurin inhibitor (CNI) toxicity was diagnosed by the typical features of pathologic findings, including arteriolar hyalinosis, isometric vacuolization of proximal tubular cells, and/or chronic medial hyaline deposits, all of which were not explained by other possible causes [8]. The diagnosis of BK virus–associated nephropathy (BKVAN) was confirmed by positive simian virus 40 immunohistochemical stains and the presence of viral cytopathic effects in renal tubular cells with interstitial mononuclear inflammatory cell infiltrates [9].

Information regarding the status of the donors and recipients was obtained from each patient at the time of biopsy. Renal function was assessed by the estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration formula [10]. The amount of proteinuria was adjusted by urine creatinine concentrations and expressed as a ratio of urine PCR. The institutional review board of each hospital approved this study, and informed consent was obtained from all patients. This work has been carried out in accordance with Declaration of Helsinki.

Statistical Analysis

All statistical analyses were performed with SPSS 20.0 (IBM, Armonk, NY). Baseline demographics and clinical parameters are expressed as mean (SD) or the number of patients (percentages), as appropriate. Analysis of variance with the Bonferroni post hoc test and χ^2 test were used for between-group comparisons. Banff pathologic scores are expressed as median (25th, 75th interquartile ranges); P values less than .05 were considered statistically significant.

RESULTS

A total of 410 indication biopsies were performed in 321 KT recipients during the study period. Samples were classified into 4 groups based on the post-transplant biopsy time point; early biopsy (<1 year post transplant; n = 184), intermediate biopsy (1-5 years post transplant; n = 120), late biopsy (5-10 years post transplant; n = 63), and very late biopsy group (>10 years post transplant; n = 43). Their baseline clinical characteristics and between-group comparisons are shown in Table 1. The mean post-transplant period was 123, 978, 2653, and 5388 days in the early, intermediate, late, and very late biopsy groups, respectively. Patients in the very late biopsy group were older and showed a female predominance. For patients with less than 5-year post-transplant duration, most graft biopsies were performed for the evaluation of unexplained elevation in serum creatinine. The proportion of those who underwent graft biopsy because of persistent proteinuria increased over time, from 0.5% in early to 16.3% in very late groups. Living donor KT was also more commonly performed in this group. Steroids and tacrolimus were less frequently prescribed to those who underwent KT more than 5 years before graft biopsy. However, these patients were more frequently taking cyclosporine; the overall prescription rate of CNIs was 90% or higher for all groups. Mean eGFR was lowest in the late biopsy group, although statistical significance was found between the intermediate and late biopsy groups only (39.9 [standard deviation {SD}, 17.5] vs 36.1 [SD, 17.5] vs 31.9 [SD, 17.9] vs 32.7 [SD, 19.8] mL/min/1.73 m^2, early vs intermediate vs late vs very late biopsy groups, respectively; $P = .006$). Finally, mean urine PCR showed a tendency to increase in patients whose post-transplant periods were long (504 [SD, 1111] vs 1570 [SD, 2843] vs 1890 [SD, 2566] vs 2420 [SD, 2432] mg/gCr, early vs intermediate vs late vs very late biopsy groups, respectively; $P = .14$).

Next, we analyzed the distributions of pathologic diagnoses according to the biopsy time point (Fig 1). The most common cause of transplant dysfunction within 1 year after KT was acute TCMR, followed by ABMR, borderline rejection, BKVAN, and CNI toxicity. Thereafter, the incidence of TCMR, borderline rejection, and BKVAN decreased over time. On the other hand, ABMR, interstitial fibrosis and tubular atrophy (IFTA), and glomerulonephritis

Table 1. Baseline Clinical Characteristics of Enrolled Patients According to Post-transplant Duration

	Early Biopsy (<1 y)	Intermediate Biopsy (1-5 y)	Late Biopsy (5-10 y)	Very Late Biopsy (>10 y)	*P* Value
Samples, No.	184	120	63	43	-
Post-transplant period, mean (SD), d	123 (102)	978 (431)	2653 (586)	5388 (1414)	-
Age, mean (SD), y	46.0 (13.4)	47.0 (11.3)	47.2 (10.6)	53.2 (10.1)	.006‡,‖
Sex, No. (%), male	135 (73.4)	81 (67.5)	34 (54.0)	20 (46.5)	<.001†,‡,‖
Indication for biopsy, No. (%)					<.001*,†,‡,§,‖
Elevated serum creatinine	183 (99.5)	112 (93.3)	51 (81.0)	36 (83.7)	
Proteinuria	1 (0.5)	8 (6.7)	12 (19.0)	7 (16.3)	
Types of donor, No. (%)					.03‡,‖
Living	101 (54.9)	70 (58.3)	40 (63.5)	34 (79.1)	
Deceased	83 (45.1)	50 (41.7)	23 (36.5)	9 (20.9)	
ABO-incompatible KT	26 (14.2)	16 (13.7)	4 (6.3)	3 (7.0)	.25
HLA mismatching, mean (SD), No.	3.4 (1.7)	3.5 (1.7)	3.3 (1.7)	3.0 (1.4)	.57
Maintenance immunosuppression, No. (%)					
Steroid	181 (98.4)	103 (85.8)	53 (84.1)	32 (74.4)	<.001*,†,‡
Tacrolimus	161 (87.5)	91 (75.8)	51 (81.0)	24 (55.8)	<.001*,‡,‖,¶
Cyclosporine	18 (9.8)	19 (15.8)	9 (14.3)	18 (41.9)	<.001*,‡,¶
Mycophenolate mofetil	150 (81.5)	102 (85.0)	51 (81.0)	34 (79.1)	.79
mTOR inhibitor	8 (4.3)	15 (12.5)	4 (8.3)	1 (2.3)	.94
eGFR, mean (SD), mL/min/1.73 m^2	39.9 (17.5)	36.1 (17.5)	31.9 (17.9)	32.7 (19.8)	.006†
Hematuria, No. (%)					.17
0-1/HPF	78 (42.4)	44 (36.7)	20 (31.7)	10 (23.3)	
2-4/HPF	46 (25.0)	30 (25.0)	14 (22.2)	16 (37.2)	
>5/HPF	60 (32.6)	46 (38.3)	29 (46.0)	17 (39.5)	
Urine PCR, mean (SD), mg/gCr	504 (1111)	1570 (2843)	1890 (2566)	2420 (2432)	.14
Donor information					
Age, mean (SD), y	51.9 (11.4)	48.9 (12.6)	41.9 (14.4)	33.9 (18.6)	<.001†,‡,§,‖,¶
Sex, No (%), male	91 (49.5)	63 (52.5)	29 (46.0)	29 (67.4)	.14

Abbreviations: eGFR, estimated glomerular filtration rate; HPF, high power field; KT, kidney transplant; mTOR, mammalian target of rapamycin; PCR, protein-to-creatinine ratio.
*$P < .05$, early vs intermediate.
†$P < .05$, early vs late.
‡$P < .05$, early vs very late.
§$P < .05$, intermediate vs late.
‖$P < .05$, intermediate vs very late.
¶$P < .05$, late vs very late.

were more frequently diagnosed in the late and very late biopsy groups. Banff pathologic scores of each diagnostic group are summarized in Table 2. As expected, biopsy samples obtained at more than 5 years post transplant showed a tendency toward chronic tubulointerstitial injuries. Notably, a substantial portion of patients diagnosed as having either TCMR or acute ABMR in the late and very late graft biopsy groups also showed pathologic evidence of interstitial fibrosis and tubular atrophy. We next analyzed the correlation between various clinical parameters and chronic interstitial fibrosis and tubular atrophy. As shown in Table 3, patients with severe chronic tubulointerstitial fibrosis exhibited significantly low eGFR and high urine PCR.

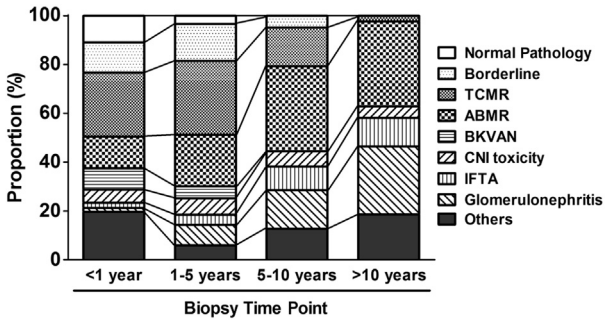

Fig 1. ABMR, antibody-mediated rejection; BKVAN, BK virus–associated nephropathy; CNI, calcineurin inhibitor; IFTA, interstitial fibrosis and tubular atrophy; TCMR, T cell–mediated rejection.

Finally, the amount of proteinuria was compared across the different diagnostic groups (Fig 2). In patients whose post-transplant period was less than 5 years, urine PCR was significantly higher in the groups with glomerulonephritis than in the others (Fig 2A). Patients with chronic active ABMR also showed a high urine PCR compared with those with borderline rejection and BKVAN. In contrast, patients who underwent graft biopsy more than 5 years after KT showed significantly high levels of proteinuria irrespective of the pathologic diagnosis, and there was no statistical difference between groups (Fig 2B). In addition, the presence of hematuria was not different across the diagnostic groups (data not shown), indicating

Table 2. Banff Pathologic Scores of Patients According to Pathologic Diagnosis and Post-transplant Duration

	<5 y Post Transplant									>5 y Post Transplant					
	NP	Borderline	TCMR	aABMR	cABMR	BKVAN	CNI Toxicity	IFTA	GN	TCMR	aABMR	cABMR	CNI Toxicity	IFTA	GN
t	0 (0, 0)	1 (1, 2)	2 (2, 3)	0 (0, 1)	0 (0, 1)	1 (1, 3)	0 (0, 0)	0 (0, 1)	0 (0, 1)	1 (1, 2)	1 (0, 1)	0 (0, 1)	0 (0, 0)	0 (0, 1)	0 (0, 1)
v	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 1)	0 (0, 1)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
i	0 (0, 0)	1 (0, 1)	2 (2, 3)	0 (0, 1)	1 (0, 2)	1 (0, 2)	0 (0, 1)	1 (0, 2)	0 (0, 2)	2 (2, 3)	0 (0, 2)	1 (1, 2)	1 (0, 1)	1 (0, 2)	1 (1, 2)
g	0 (0, 0)	0 (0, 0)	0 (0, 1)	2 (1, 3)	0 (0, 3)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 1)	2 (1, 3)	3 (1, 3)	0 (0, 0)	0 (0, 1)	0 (0, 0)
ci	0 (0, 0)	0 (0, 1)	0 (0, 1)	0 (0, 1)	1 (0, 2)	0 (0, 1)	1 (0, 1)	2 (1, 3)	0 (0, 1)	1 (1, 2)	1 (1, 2)	2 (1, 2)	1 (1, 1)	2 (1, 3)	1 (1, 2)
ct	0 (0, 0)	0 (0, 1)	1 (0, 1)	0 (0, 2)	1 (0, 1)	0 (0, 1)	1 (0, 1)	2 (1, 3)	1 (0, 1)	1 (1, 2)	1 (1, 2)	2 (1, 2)	1 (1, 2)	3 (1, 3)	2 (1, 2)
cg	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 2)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	3 (2, 3)	0 (0, 0)	0 (0, 0)	0 (0, 0)
mm	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 1)	0 (0, 0)	0 (0, 0)	0 (0, 1)	0 (0, 0)	1 (0, 1)	0 (0, 0)	1 (0, 1)	0 (0, 1)	0 (0, 1)	2 (0, 2)
cv	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 1)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 1)	0 (0, 0)	0 (0, 2)	0 (0, 2)	0 (0, 0)	0 (0, 2)	0 (0, 0)	0 (0, 0)
ah	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	1 (0, 2)	0 (0, 1)	0 (0, 0)	0 (0, 1)	0 (0, 2)	2 (1, 3)	3 (3, 3)	1 (0, 2)	0 (0, 2)
ptc	0 (0, 0)	0 (0, 0)	0 (0, 1)	2 (1, 2)	1 (0, 2)	0 (0, 0)	0 (0, 0)	0 (0, 1)	0 (0, 0)	0 (0, 1)	1 (0, 3)	2 (2, 3)	0 (0, 0)	0 (0, 0)	0 (0, 2)

Data are expressed as median (25th, 75th interquartile range).

Abbreviations: aABMR, acute antibody-mediated rejection; BKVAN, BK virus–associated nephropathy; cABMR, chronic active antibody-mediated rejection; CNI, calcineurin inhibitor; GN, glomerulonephritis; IFTA, interstitial fibrosis and tubular atrophy; NP, normal pathology; TCMR, T cell–mediated rejection.

Banff pathologic scores: ah, arterial hyalinosis; cg, transplant glomerulopathy; ci, interstitial fibrosis; ct, tubular atrophy; cv, vascular fibrous intimal thickening; g, glomerulitis; i, interstitial inflammation; mm, mesangial matrix expansion; ptc, peritubular capillaritis; t, tubulitis; v, intimal arteritis.

Table 3. Correlation Between Clinical Parameters and Interstitial Fibrosis/Tubular Atrophy

	Interstitial Fibrosis Score					Tubular Atrophy Score				
	0	1	2	3	*P* Value	0	1	2	3	*P* Value
Age, mean (SD), y	46.6 (12.9)	48.0 (11.5)	47.4 (13.0)	47.9 (10.3)	.77	47.3 (13.1)	46.8 (11.8)	47.9 (12.2)	47.6 (10.4)	.84
Sex, No. (%), male	128 (69.6)	84 (64.6)	35 (59.3)	17 (60.7)	.45	118 (70.7)	90 (65.7)	39 (60.0)	17 (53.1)	.17
Post-transplant period, mean (SD), d	500 (877)	1930 (2053)	2150 (1905)	2260 (1835)	< .001[*,†,‡]	472 (946)	1623 (1771)	2290 (2072)	2596 (2029)	< .001[*,†,‡,§,‖]
Living donor KT, No. (%)	111 (60.3)	84 (64.6)	31 (52.5)	16 (57.1)	.46	103 (61.7)	87 (63.5)	34 (52.3)	18 (56.2)	.44
ABO incompatible KT, No. (%)	28 (15.2)	14 (10.9)	6 (10.3)	1 (3.6)	.28	26 (15.6)	16 (11.9)	5 (7.7)	2 (6.2)	.26
HLA mismatching, mean (SD), No.	3.4 (1.6)	3.6 (1.5)	3.3 (1.7)	3.4 (1.7)	.56	3.5 (1.6)	3.4 (1.6)	3.3 (1.6)	3.6 (1.8)	.75
eGFR, mean (SD), mL/min/1.73 m^2	40.9 (18.1)	36.7 (18.0)	29.7 (14.9)	25.5 (17.4)	< .001[†,‡,‖]	40.9 (17.9)	38.2 (18.2)	30.1 (16.4)	23.0 (12.5)	< .001[†,‡,§,‖]
Urine PCR, mean (SD), mg/gCr	652 (1805)	1612 (2540)	1978 (1986)	1831 (1986)	< .001[*,†,‡]	530 (1408)	1570 (2490)	2157 (3062)	1681 (1752)	< .001[*,†,‡]

Abbreviations: eGFR, estimated glomerular filtration rate; KT, kidney transplant; PCR, protein-to-creatinine ratio.
[*] $P < .05$, grade 0 vs 1.
[†] $P < .05$, grade 0 vs 2.
[‡] $P < .05$, grade 0 vs 3.
[§] $P < .05$, grade 1 vs 2.
[‖] $P < .05$, grade 1 vs 3.

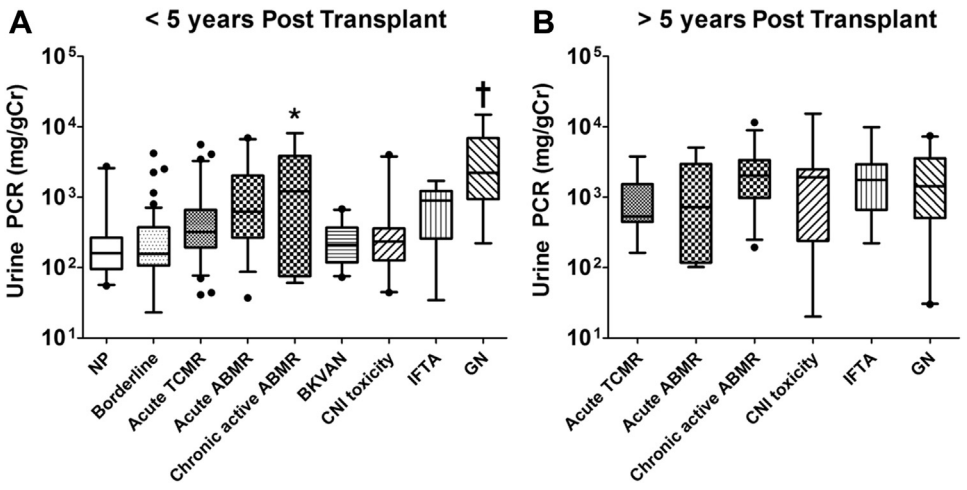

Fig 2. ABMR, antibody-mediated rejection; BKVAN, BK virus–associated nephropathy; CNI, calcineurin inhibitor; GN, glomerulonephritis; IFTA, interstitial fibrosis and tubular atrophy; NP, normal pathology; PCR, protein-to-creatinine ratio; TCMR, T cell–mediated rejection.

that the post-transplant period is an important factor for the accurate interpretation of urine test results in KT recipients.

DISCUSSION

With the advances in immunosuppressive drugs, short-term graft outcomes after KT have greatly improved over the last few decades. However, this has not translated into notable improvements in long-term graft outcomes, suggesting that there are distinct mechanisms underlying early and late graft dysfunction. Consistently, we identified several significant differences in clinicopathologic features among patients with different biopsy time points after KT. Considering that most biopsy samples obtained more than 5 years after KT exhibited chronic IFTA in the present study (Table 2), more investigations are needed to clarify the early pathophysiologic events that trigger late chronic tubulointerstitial changes to make further improvements in the long-term preservation of graft function.

The distribution of pathologic diagnoses was significantly altered over time (Fig 1). The overall trends were similar to those described in previous report by Halloran et al [1]. The prevalence of ABMR, IFTA, and glomerulonephritis increased whereas that of normal pathology, TCMR, and BKVAN decreased in the late graft biopsy group compared with the early biopsy group. Of these, the decrease in the incidence of TCMR was dramatic, from a prevalence of 26.1% in the early biopsy group to that of 2.3% in the very late biopsy group. Interestingly, a substantial proportion of patients diagnosed as having TCMR more than 5 years after KT showed concurrent evidence of chronic tubulointerstitial injuries (Table 2). Moreover, 66.7% (14/21) of patients diagnosed as having IFTA in this period also showed active tubulointerstitial inflammation, although the degree of inflammation was mostly mild (Table 2). The recently published 2017 Banff Kidney Meeting Report included "chronic active TCMR" as a new diagnostic category, which is characterized by both active tubulointerstitial inflammation (tubulitis and interstitial inflammation) and IFTA [11]. In this study, no patient was diagnosed as having chronic active TCMR because the pathologic diagnoses were in accordance with 2007 Banff classification [7], in which the concept of chronic active TCMR is not mentioned. On review of the Banff pathologic scores, 36.7% (8/22) of patients with TCMR or IFTA in the late and very late graft biopsy groups should have been diagnosed as having chronic active TCMR based on the 2017 Banff classification. Besides the well-documented role of ABMR, we believe that chronic active TCMR may be another important but underestimated contributor to late graft failure.

CNI toxicity accounted for about 5% to 10% of the graft dysfunction in this study. Although tacrolimus, which is the CNI much more frequently prescribed as a maintenance immunosuppressant, has been reported to be less nephrotoxic than cyclosporine [12,13], there are still concerns regarding its renal safety, especially with respect to chronic tubulointerstitial fibrosis. Notably, CNI toxicity in late graft biopsy specimens has been mostly confirmed by chronic medial arteriolar hyalinosis, which is a typical feature of chronic CNI toxicity [14]. Given that chronic CNI toxicity manifests as nonspecific pathology, such as nonspecific IFTA, global glomerulosclerosis, or even secondary focal segmental glomerulosclerosis [14], the importance of CNI toxicity may be greater than we speculate in clinical practice.

Post-transplant proteinuria is a relatively common phenomenon, especially for a month after KT [15]. Early posttransplant proteinuria typically resolves spontaneously, while persistent proteinuria signifies worsening graft survival [16]. Several investigations have documented the relationship between the levels of proteinuria and pathologic diagnosis; overt proteinuria, usually defined as >1000 mg/d, is

mostly associated with glomerular pathology, including glomerulonephritis and transplant glomerulopathy [17,18]. However, these studies analyzed graft biopsy samples obtained within the first year after KT. Therefore, it was unclear whether these results could be generalized to the interpretation of graft biopsy specimens obtained in late post-transplant period. Our data indicate that although the distribution patterns of proteinuria according to the pathologic diagnosis were comparable with those in previous studies analyzing patients who underwent graft biopsy less than 5 years post transplant, these relationships were profoundly altered in those who underwent biopsy more than 5 years post transplant (Fig 2). Interestingly, evidence of chronic glomerular injury was only observed in patients at more than 5 years post transplant, except for the chronic active ABMR group, despite the relatively high levels of proteinuria in these patients (Table 2). These results suggest that chronic tubulointerstitial damage may be a secondary phenomenon due to significant proteinuria. Therefore, we speculate that while the presence of proteinuria early after KT indicates specific pathologic conditions, its presence late after KT could be nonspecific. Further studies are needed to determine whether proteinuria in the late post-transplant period retains a relevant association with graft outcomes.

In conclusion, we demonstrated that the etiology of graft dysfunction is largely influenced by biopsy time point. A better understanding of the exact pathophysiologic mechanisms of late graft dysfunction is mandatory to achieve further improvements in long-term graft outcomes after KT.

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