의학석사 학위논문

Incidence of Posttransplant Glomerulonephritis and Its Impact on Graft Outcome

이식 후 사구체신염의 발생률과 이식 신에 미치는 영향에 대한 연구

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Abstract

Introduction: Herein, the significance of post-transplant glomerulonephritis (PTGN) has been revisited to investigate whether PTGN induces allograft failure. The aim of this study was to identify the incidence of PTGN and its association with allograft failure, as well as to analyze the risk factors for PTGN.

Methods: Among 996 patients who underwent kidney transplantation in a multicenter cohort from 1995 to 2010, 764 patients were enrolled in this study.

Results: The incidence rate of PTGN was 9.7% and 17.0% at 5 and 10 years of follow-up, respectively. PTGN was diagnosed in 17.8% of the recipients with results of biopsy tests or clinical diagnosis identifying glomerular diseases as the underlying cause, compared with 0.0%, 4.4%, 4.9%, 5.5%, and 5.7% of the recipients with renal vascular diseases, renal interstitial diseases/pyelonephritis/uropathy, diabetic renal disease, hereditary renal diseases, and diseases with unknown etiologies, respectively. Allograft survival was significantly decreased in patients with PTGN. PTGN was associated with a fourfold increase in graft failure with a hazard ratio of 7.11 for both acute rejection and PTGN. Results of the risk factor analysis for PTGN revealed that the underlying glomerular renal diseases and treatment

methods using drugs such as tacrolimus and basiliximab significantly increased PTGN development, after adjusting for other risk factors.

Conclusion: We conclude that PTGN is strongly associated with poor kidney allograft survival. Therefore, optimal management of recurrent or de novo GN should be the critical focus of post-transplant care.

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Keywords: Kidney transplantation, Glomerulonephritis, Risk factors, Graft survival

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Introduction

Chronic glomerulonephritis (GN) is one of the main etiologies of end-stage renal disease (ESRD), and the indication for kidney transplantation in 30-50% of recipients (1). Although much improvement in immunosuppression regimens has been achieved in the past 20 years, long-term allograft outcome has not significantly improved (2-4).

Along with the major impact of interstitial fibrosis, tubular atrophy, and chronic rejection on allograft outcome, recurrence or *de novo* development of glomerulonephritis (posttransplant glomerulonephritis, PTGN) may be one of the factors affecting long-term outcome (5, 6).

GN of all types may recur or develop soon after kidney transplantation; the prevalence of PTGN depends upon the original underlying kidney disease: 20-50% in membranoproliferative GN (MPGN) Type I, 80-100% in MPGN Type II, 20-50% in focal segmental glomerulosclerosis (FSGS), 13-50% in immunoglobulin A nephropathy (IgAN), and 10-30% in membranous nephropathy (MN) (7).

Our recent work highlights the significant effect of IgAN recurrence on allograft outcome, specifically that chronic changes negatively affected allograft outcome more significantly than IgAN recurrence (8). Though the data are limited, the development of various PTGN and kidney allograft failure due to PTGN has been reported in patients with underlying chronic GN (9-11). On the other hand, many chronic kidney disease patients with

unknown etiology progress to ESRD and have renal transplants. Allograft outcome in these groups with PTGN has not been investigated thoroughly.

We aimed to investigate and identify the incidence, risk factors, and the effect on graft survival of PTGN not only in patients with chronic GN, but in patients with ESRD of unknown etiology.

Materials and Methods

Study population

We enrolled 764 of 996 patients who underwent kidney transplantation at Seoul National University Hospital, Seoul National University Bundang Hospital, and Seoul National University Boramae Medical Center between 1995 and 2010. Patients under age 18 and those who were retransplanted or underwent multiorgan transplantation were excluded from the study. This study was approved by the Seoul National University Hospital Institutional Review Board. All clinical investigations were conducted in accordance with the guidelines of the 2008 Declaration of Helsinki.

Data collection

Patient gender, age, comorbidities, donor type, human leukocyte antigen (HLA) status, original kidney disease, date of referral, date of transplantation, and immunosuppressant regimens were recorded. Original kidney diseases were classified into six groups: glomerular diseases, renal vascular diseases, renal interstitial diseases/PN/uropathy, diabetic renal disease, hereditary renal diseases, and unknown etiologies. They were diagnosed by kidney biopsy, or imaging studies such as computed tomography, magnetic resonance imaging, and kidney ultrasonography, or clinical judgments by physicians and researchers. Early referral was defined as the interval between the nephrologist’s visit and the diagnosis of ESRD or the start of renal

replacement therapy for longer than 1 year.

Hypertension was defined as a systolic blood pressure greater than or equal to 140 mmHg, diastolic pressure greater than or equal to 90 mmHg, or the concurrent use of antihypertensive medications. Diabetes mellitus was diagnosed in patients with a random blood glucose concentration of greater than or equal to 200 mg/dl, fasting plasma glucose of greater than or equal to 126 mg/dl on at least two separate occasions, or patients using anti-hyperglycemic medications.

Clinical parameters that could have influenced the development of PTGN were collected at the time of kidney biopsy, i.e., serum creatinine, estimated glomerular filtration rate (eGFR), hematuria, and daily proteinuria. Serum creatinine levels were measured with an assay based on the Jaffe' method and eGFR was calculated using an abbreviated MDRD (Modification of Diet in Renal Disease formula) formula: GFR (ml/min/1.73 m^2) = 186 x $(S_{cr})^{1.154}$ x (age in years)$^{-0.203}$ x (0.742 if female).

PTGN and graft outcome

Allograft biopsies were performed when the eGFR fell below 60 ml/min or clinically significant hematuria (gross hematuria or RBC ≥ 5/HPF in urinalysis and microscopy) or proteinuria (random urine protein/creatinine ratio (PCR) over 0.5) developed. All protocol biopsies were excluded from the study. Acute rejection or PTGN was diagnosed by accurate histological classification, via kidney biopsy. Biopsy-unproven cases with clinical

indications above-mentioned were not classified as PTGN. The date of diagnosis of PTGN was recorded as the date of biopsy. Graft failure was defined as the requirement for permanent dialysis or allograft nephrectomy, retransplantation, and censoring the recipient's death.

Immunosuppressive treatment protocols

A standardized immunosuppression protocol involving a combination of a calcineurin inhibitor and steroids was initiated within 24 hours of surgery. The choice of calcineurin inhibitor, either cyclosporine A (CsA) or tacrolimus was determined by the transplantation team. The initial dose of CsA was 10 mg/kg per day by the oral route; target trough levels were 200–400 ng/mL during the first 4 weeks and 100–200 ng/mL thereafter. The initial dose of tacrolimus was 0.16 mg/kg per day by the oral route; target trough levels were 8–15 ng/mL during the first 3 months and 3–8 ng/mL thereafter. Methylprednisolone (1 g/day) was administered by intravenous infusion on the day of transplantation and tapered to prednisone at 30 mg/day on posttransplantation day four, and then administered at maintenance dose without withdrawal. Purine synthesis inhibitors such as mycophenolate mofetil (MMF) were used as an initial immunosuppressive treatment based on clinical judgment considering risk factors such as HLA mismatch.

Statistical analysis

We compared the categorical variables with the chi-square test; and

continuous variables expressed as the mean ± standard deviation were compared by the Student's *t*-test or One-way analysis of variance (ANOVA). The Kaplan-Meier method was used to estimate the incidence of PTGN and graft failure and to compare cumulative probability of PTGN with several risk factors (log-rank test). The effect of PTGN on death-censored graft failure was also evaluated by Kaplan-Meier analysis. Cox proportional hazard models were used to examine the association between multiple risk factors and PTGN occurrence. In multivariate analysis, statistically significant covariates from the univariate analysis ($p < 0.01$) were selected. A p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 18.0K software (SPSS Inc., Chicago, IL, USA).

Results

Patient demographics

Patient demographics are shown in Table 1. Mean duration of follow up was 60.71 ± 50.77 (range 0.4 to 182.5) months. Among 764 recipients, 292 (38.2%) had biopsy-proven or clinically diagnosed glomerular diseases and 131 (17.1%), 45 (5.9%), 82 (10.7%), and 73 (9.6%) were classified as renal vascular diseases, renal interstitial diseases / pyelonephritis (PN) / uropathy, diabetic renal disease, and hereditary renal diseases, respectively. The remaining 141 (18.5%) patients underwent kidney transplantation due to renal failure caused by unknown etiologies. Of the 292 patients in the glomerular diseases group, histological confirmation was performed in 195 (66.8%) patients. The results of which are as follows: 66.1% of the patients are with IgAN, 8.2% with FSGS, 7.2% with lupus nephritis, 4.1% with MPGN, 2.1% with MN, and 12.3% with other GN (Table 2).

Regarding donor type, living related donors were the most common, followed by deceased and living unrelated donors. 569 (74.5%) patients were referred early to nephrologists. 274 patients (35.9%) received preemptive transplantation. Tacrolimus and CsA were administered to 50.9% and 48.3% of recipients, and 42.1% received basiliximab pre-transplantation. Among the antimetabolite antirejection drugs, MMF was the most common (75.1%).

Table 1. Baseline Characteristics with Classified by Underlying Kidney Disease

	Total (N=764)	Glomerular (N=292, 38.2%)	Vascular (N=131, 17.1%)	Interstitial/ PN/Uropathy (N=45, 5.9%)	Diabetic (N=82, 10.7%)	Hereditary & various (N=73, 9.6%)	Unknown (N=141, 18.5%)
Era							
1995 - 2000	173 (22.6)	72 (24.7)	33 (25.2)	12 (26.7)	4 (4.9)	13 (17.8)	39 (27.7)
2001 - 2005	235 (30.8)	89 (30.5)	45 (34.4)	15 (33.3)	23 (28.0)	19 (26.0)	44 (31.2)
2006 - 2010	356 (46.6)	131 (44.8)	53 (40.4)	18 (40.0)	55 (67.1)	41 (56.2)	58 (41.1)
HLA mismatch							
Unknown	22 (2.9)	8 (2.7)	0 (0)	0 (0)	4 (4.9)	1 (1.4)	9 (6.4)
0	100 (13.1)	44 (15.1)	13 (9.9)	10 (22.2)	6 (7.3)	7 (9.6)	20 (14.2)
1 - 3	410 (53.7)	162 (55.5)	77 (58.8)	23 (51.1)	40 (48.8)	33 (45.2)	75 (53.2)
4 - 6	232 (30.3)	78 (26.7)	41 (31.3)	12 (26.7)	32 (39.0)	32 (43.8)	37 (26.2)
Male (Recipient)	446 (58.4)	167 (57.2)	83 (63.4)	24 (53.3)	55 (67.1)	45 (61.6)	72 (51.1)
Male (Donor)	406 (54.0)	161 (56.1)	77 (58.8)	21 (46.7)	42 (52.5)	42 (57.5)	63 (46.3)
Donor type							
Living related	451 (59.0)	190 (65.1)	75 (57.3)	27 (60.0)	43 (52.4)	34 (46.6)	82 (58.2)
Living unrelated	141 (18.5)	42 (14.4)	35 (26.7)	4 (8.9)	18 (22.0)	18 (24.7)	24 (17.0)
Deceased	172 (22.5)	60 (20.5)	21 (16.0)	14 (31.1)	21 (25.6)	21 (28.7)	35 (24.8)
Referral							
Early (≥1yr)	569 (74.5)	249 (85.3)	71 (54.2)	41 (91.1)	78 (95.2)	70 (95.9)	60 (42.6)

Late (<1yr)	178 (23.3)	38 (13.0)	54 (41.2)	4 (8.9)	2 (2.4)	3 (4.1)	77 (54.6)
Unknown	17 (2.2)	5 (1.7)	6 (4.6)	0 (0)	2 (2.4)	0 (0)	4 (2.8)
Preemptive	274 (35.9)	113 (38.7)	50 (38.2)	10 (22.2)	22 (26.8)	29 (39.7)	50 (35.5)
Diabetes mellitus	93 (12.2)	3 (1.0)	2 (1.5)	1 (2.2)	82 (100.0)	3 (4.1)	2 (1.4)
Hypertension	523 (68.5)	192 (65.8)	131 (100.0)	20 (44.4)	58 (70.7)	33 (45.2)	89 (63.1)
Immunosuppressants							
Calcineurin inhibitors							
Cyclosporine A	369 (48.3)	137 (46.9)	71 (54.2)	20 (44.4)	42 (51.2)	27 (37.0)	72 (51.1)
Tacrolimus	389 (50.9)	155 (53.1)	58 (44.3)	24 (53.4)	38 (46.4)	46 (63.0)	68 (48.2)
Others	6 (0.8)	0 (0)	2 (1.5)	1 (2.2)	2 (2.4)	0 (0)	1 (0.7)
Purine synthesis inhibitors							
Not use	82 (10.7)	35 (12.0)	17 (13.0)	5 (11.1)	2 (2.4)	8 (11.0)	15 (10.6)
MMF	574 (75.2)	215 (73.6)	90 (68.7)	34 (75.6)	77 (93.9)	56 (76.7)	102 (72.3)
Azathioprine	107 (14.0)	41 (14.0)	24 (18.3)	6 (13.3)	3 (3.7)	9 (12.3)	24 (17.1)
Others	1 (0.1)	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Basiliximab	322 (42.1)	115 (39.4)	50 (38.2)	20 (44.4)	46 (56.1)	38 (52.1)	53 (37.6)
Age at transplant	41.49 ± 11.97	38.69 ± 11.06	46.18 ± 10.60	35.22 ± 12.71	52.10 ± 9.18	39.84 ± 13.43	39.65 ± 10.46
Donor age	38.80 ± 12.26	38.25 ± 11.71	38.58 ± 10.95	37.98 ± 12.52	40.44 ± 14.77	40.79 ± 12.92	38.38 ± 12.57

Most numerical values are expressed as mean ± standard deviation

PN, pyelonephritis; HLA, human leukocyte antigen; MMF, mycophenolate mofetil

Table 2. Association between underlying kidney diseases and the incidence of PTGN

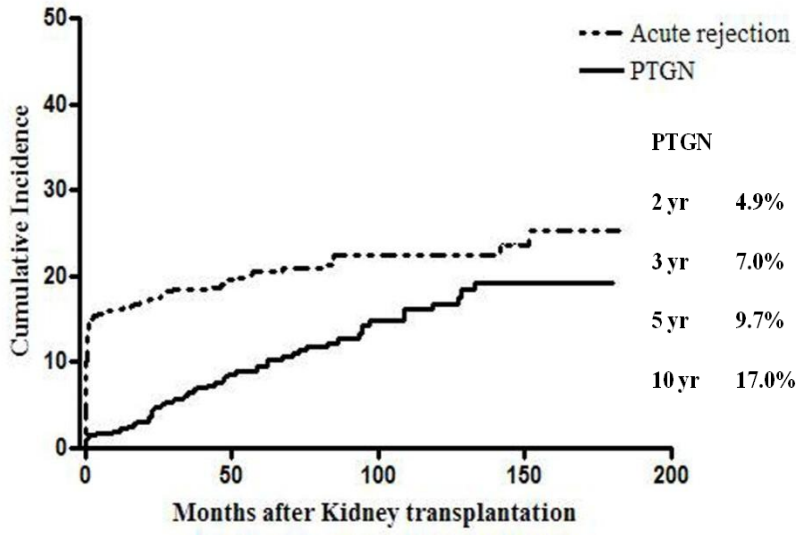
Underlying kidney disease	N	Patients with PTGN						
		IgAN	FSGS	MPGN	MN	Immune-mediated GN	Lupus nephritis	Incidence of PTGN (%)[1]
Glomerular	292	42	4	2	1	2	1	52 (17.8)
Biopsy-proven								
IgAN	129	19	1	0	0	0	0	20 (15.5)
FSGS	16	4	1	0	0	0	0	5 (31.3)
MPGN	8	0	0	1	0	1	0	2 (25.0)
MN	4	0	0	0	0	0	0	0 (0.0)
Lupus nephritis	14	0	0	0	0	0	1	1 (7.1)
Other GN	24	0	1	1	0	0	0	2 (8.3)
Clinical	97	19	1	0	1	1	0	22 (22.7)
Vascular	131	0	0	0	0	0	0	0 (0.0)
Interstitial/ PN/Uropathy	45	2	0	0	0	0	0	2 (4.4)
Diabetic	82	3	1	0	0	0	0	4 (4.9)
Hereditary/Various	73	1	1	1	1	0	0	4 (5.5)
Unknown	141	6	2	0	0	0	0	8 (5.7)
Total	764	54	8	3	2	2	1	70 (9.2)

[1] Incidence rate of developing PTGN in each group of underlying renal diseases; GN, glomerulonephritis; IgAN, immunoglobulin A nephropathy; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative GN; MN, membranous nephropathy; PN, pyelonephritis ; PTGN, posttransplantation glomerulonephritis

Incidence of PTGN and its impact on graft survival

At follow up, 70 (9.2%) patients were diagnosed with PTGN. At diagnosis, serum creatinine level was 1.88 ± 2.24 mg/dl, eGFR was 49.67 ± 20.97 ml/min, and random urine PCR was 2.57 ± 3.18 g (Table 3).

The incidence of PTGN increased with time after transplantation, from 4.9% at 2 years to 9.7% at 5 years, and 17.0% at 10 years. PTGN occurred steadily throughout the follow up period, while most acute rejection episodes developed early (Figure 1).



Patients at risk

Acute rejection	**764**	**417**	**273**	**165**	**101**	**85**	**46**	**0**
PTGN	**764**	**487**	**340**	**210**	**129**	**93**	**53**	**0**

Figure 1. Incidence of posttransplant glomerulonephritis (PTGN) compared to acute rejection. The incidence of PTGN increased steadily and consistently over the duration of follow up, whereas acute rejection occurred rapidly early posttransplant, and the slope decreased thereafter.

Table 3. Baseline characteristics in patients with diagnosed PTGN of each period

	Total (N=70)	1995-2000 (N=24)	2001-2005 (N=27)	2006-2010 (N=19)	P
Underlying kidney disease					
Glomerular	52 (74.3)	17 (70.8)	21 (77.8)	14 (73.7)	.943
Vascular	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	.943
Interstitial/PN/Uropathy	2 (2.0)	1 (4.2)	1 (3.7)	0 (0.0)	.943
Diabetic	4 (5.7)	1 (4.2)	2 (7.4)	1 (5.3)	.943
Hereditary/Various	4 (5.7)	2 (8.3)	1 (3.7)	1 (5.3)	.943
Unknown	8 (11.4)	3 (12.5)	2 (7.4)	3 (15.8)	.943
HLA mismatch					
0	11 (15.7)	3 (12.5)	6 (22.2)	2 (10.5)	.278
1 - 3	38 (54.3)	15 (62.5)	15 (55.6)	8 (42.1)	.278
4 - 6	21 (30.0)	6 (25.0)	6 (22.2)	9 (47.4)	.278
Age at transplant (years)	38.20±11.34	36.71±11.25	37.22±11.53	41.47±11.09	.337
Donor age (years)	36.01±11.12	32.71±11.02	36.33±10.53	39.71±11.39	.118
Male Gender (Recipient)	37 (52.9)	15 (62.5)	16 (59.3)	6 (31.6)	.091
Male Gender (Donor)	38 (54.3)	14 (58.3)	13 (48.1)	11 (57.9)	.716
Donor type					
Living related	42 (60.0)	17 (70.8)	18 (66.7)	7 (36.8)	.016
Living unrelated	12 (17.1)	3 (12.5)	6 (22.2)	3 (15.8)	.016
Deceased	16 (22.9)	4 (16.7)	3 (11.1)	9 (47.4)	.016
Referral					
Late Referral	26 (37.7)	12 (50.0)	9 (34.6)	4 (21.1)	.150
Early Referral	43 (62.3)	12 (50.0)	17 (65.4)	15 (78.9)	.150

Preemptive	19 (27.1)	7 (29.2)	9 (33.3)	3 (15.8)	.404
Diabetes Mellitus	6 (9.0)	2 (9.1)	2 (7.4)	2 (11.1)	.843
Hypertension	48 (68.6)	20 (83.3)	18 (66.7)	10 (52.6)	.095
Laboratory findings					
Serum Creatinine	1.88±2.24	2.51±3.60	1.71±1.06	1.34±0.50	.211
Random urine PCR	2.57±3.18	4.21±4.36	1.79±1.83	1.40±1.75	.012
eGFR	49.67±20.97	46.52±24.29	47.60±19.99	56.60±16.89	.240
Immunosuppressant					
Calcineurin Inhibitor					
Tacrolimus	1 (2.1)	0 (0)	0 (0)	1 (9.1)	.126
Cyclosporine A	47 (97.9)	20 (100.0)	17 (100.0)	10 (90.9)	.126
Purine synthesis inhibitors					
Not use	15 (21.4)	11 (45.8)	3 (11.1)	0 (0)	.841
Azathioprine	11 (15.7)	10 (41.7)	1 (3.7)	0 (0)	.841
Mycophenolate Mofetil	44 (62.9)	3 (12.5)	23 (85.2)	19 (100.0)	.841
Basiliximab	24 (34.3)	2 (8.3)	7 (25.9)	15 (78.9)	<.001

Most numerical values are expressed as mean ± standard deviation.

PN, pyelonephritis; PTGN, posttransplantation glomerulonephritis; DM, diabetes mellitus; HTN, hypertension; GN, glomerulonephritis; HLA, human leukocyte antigen; PCR, protein/creatinine ratio; eGFR, estimated glomerular filtration rate

Concerning underlying kidney diseases, PTGN was diagnosed in 17.8% of glomerular diseases, compared to 0.0%, 4.4%, 4.9%, and 5.5% of recipients in renal vascular diseases, renal interstitial diseases/PN/uropathy, diabetic renal disease, and hereditary renal diseases group, and 5.7% of patients with unknown etiologies (Table 2). Furthermore, in the glomerular diseases group, the incidence increased more rapidly than in other groups (Figure 2). Among all PTGN, the most common type was IgAN (77.1%), followed by FSGS (8.6%) and MPGN (5.7%) (Table 2).

Allograft survival was markedly decreased in patients with PTGN ($p<0.001$) (Figure 3). When we analyzed graft survival by the incidence of PTGN and acute rejection, we found that as PTGN developed, the risk of graft failure increased 4.02 fold (95% Confidence Interval (CI) 1.74-9.29, $p=0.001$). In case of the occurrence of both acute rejection and PTGN, the hazard ratio (HR) of graft failure was 7.11 (95% CI 2.96-17.07, $p<0.001$). After adjustment for other risk factors, PTGN was the strongest risk factor for graft failure (Table 4, Figure 4).

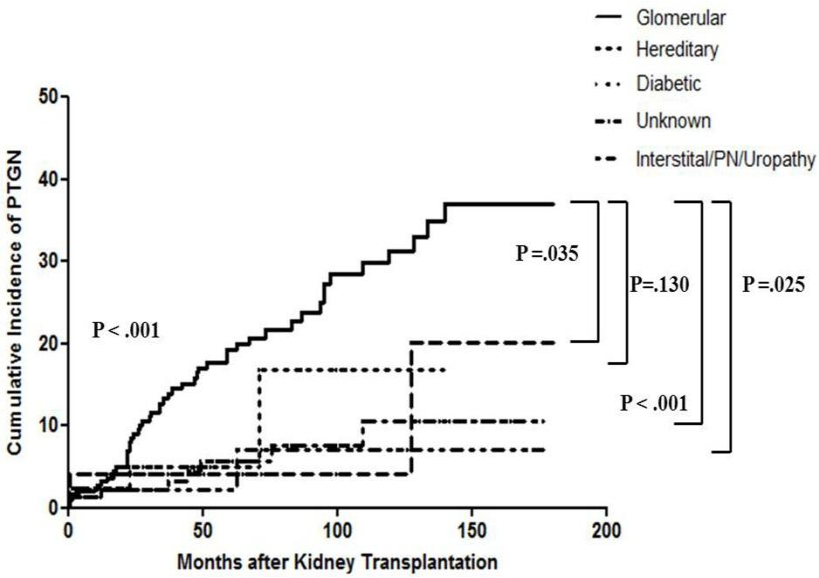


Figure 2. Association between underlying kidney disease and PTGN. In the glomerular diseases group, PTGN developed more than in other etiology groups (P<0.001). The significant difference between glomerular diseases group and unknown etiology group was specifically in the development of PTGN (P<0.001). In all groups, PTGN increased over the duration of follow up. PN, pyelonephritis; PTGN, posttransplantation glomerulonephritis

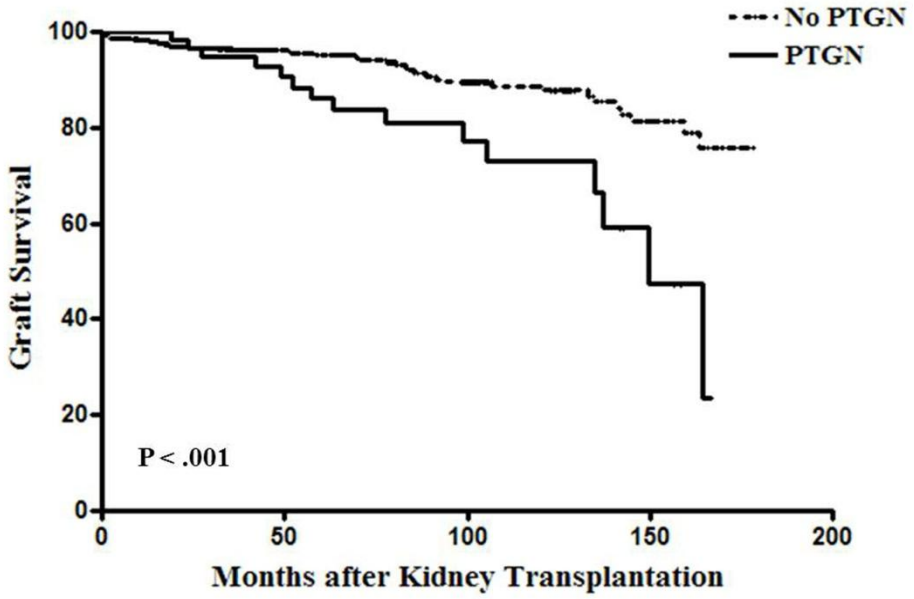


Figure 3. Association between PTGN prevalence and graft failure. The development of PTGN was an obvious risk factor for kidney allograft failure. In patients with PTGN, graft survival decreased significantly (P<0.001).

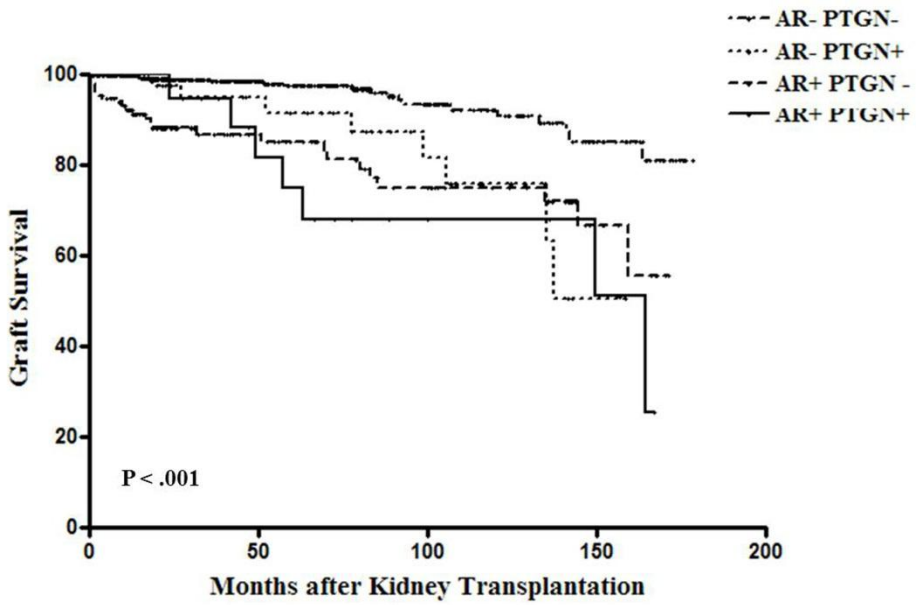


Figure 4. Effects on graft failure of acute rejection and PTGN. As PTGN developed, the incidence of graft failure increased significantly. Furthermore, the presence of both acute rejection and PTGN caused allograft failure to increase. AR, acute rejection; PTGN, posttransplantation glomerulonephritis

Table 4. Effects on graft failure of acute rejection and PTGN

		Univariate Analysis		Multivariate Analysis[1]	
	N	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Acute rejection - PTGN -	564	Reference		Reference	
Acute rejection - PTGN +	46	3.84 (1.68 – 8.77)	.001	4.02 (1.74– 9.29)	.001
Acute rejection + PTGN -	132	4.79 (2.65 – 8.65)	< .001	5.40 (2.94 – 9.93)	< .001
Acute rejection + PTGN +	22	6.22 (2.62 – 14.76)	< .001	7.11 (2.96 – 17.07)	< .001

[1] Adjusted for following variables: underlying renal diseases, the era of transplantation, HLA mismatch, age and gender of recipient and donor, donor type, timing difference of referral, preemptive transplantation, and administered immunosuppressants; PTGN, posttransplantation glomerulonephritis; HR, hazard ratio

In addition, we identified graft survival by the incidence of PTGN, acute rejection, and chronic rejection including chronic allograft nephropathy (CAN). In any combinations of the development of acute rejection and CAN, as PTGN developed, the risk of graft failure increased to a considerable extent (Table 5). However, the number of patients with the occurrence of all of them was small, so HR of graft failure seems to be underestimated.

When analyzing the effects on allograft survival of several types of PTGN, there was no significant difference between IgAN, FSGS, MPGN, and immune-mediated GN, and it was also identified by Kaplan-Meier analysis (Table 6, Figure 5).

Table 5. Effects on graft failure of acute and chronic rejection, and PTGN

		Univariate Analysis		Multivariate Analysis[1]	
	N	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Acute rejection - CAN - PTGN -	536	Reference		Reference	
Acute rejection - CAN - PTGN +	34	3.90 (1.42 – 10.69)	.008	2.71 (0.87 – 8.47)	.087
Acute rejection - CAN + PTGN -	22	3.92 (1.30 – 11.79)	.015	4.05 (1.16 – 14.20)	.029
Acute rejection - CAN + PTGN +	12	5.63 (1.63 – 19.39)	.006	5.13 (1.34 – 19.61)	.017
Acute rejection + CAN - PTGN -	98	3.85 (1.82 – 8.16)	<.001	4.66 (2.03 – 10.68)	<.001
Acute rejection + CAN - PTGN +	14	9.68 (3.76 – 24.92)	<.001	11.20 (3.81 – 32.90)	<.001
Acute rejection + CAN + PTGN -	38	8.93 (4.27 – 18.66)	<.001	9.40 (4.09 – 21.60)	<.001
Acute rejection + CAN + PTGN +	10	2.28 (0.30 – 17.21)	.426	3.62 (0.39 – 33.34)	.256

[1] Adjusted for following variables: underlying renal diseases, the era of transplantation, HLA mismatch, age and gender of recipient and donor, donor type, timing difference of referral, preemptive transplantation, and administered immunosuppressants

CAN, chronic allograft nephropathy; PTGN, posttransplantation glomerulonephritis; HR, hazard ratio

Table 6. Effects on graft failure of the type of PTGN

	Patients with graft failure		
	N (%)	**HR (95% CI)**	***P***
IgAN	11/54 (20.4%)	Reference	
FSGS	2/8 (25%)	1.48 (0.32 – 6.89)	0.615
MPGN	1/3 (33.3%)	1.08 (0.13 – 8.78)	0.945
Immune-mediated GN	1/2 (50%)	3.20 (0.40 – 25.84)	0.275

IgAN, immunoglobulin A nephropathy; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; GN, glomerulonephritis; PTGN, posttransplantation glomerulonephritis; HR, hazard ratio

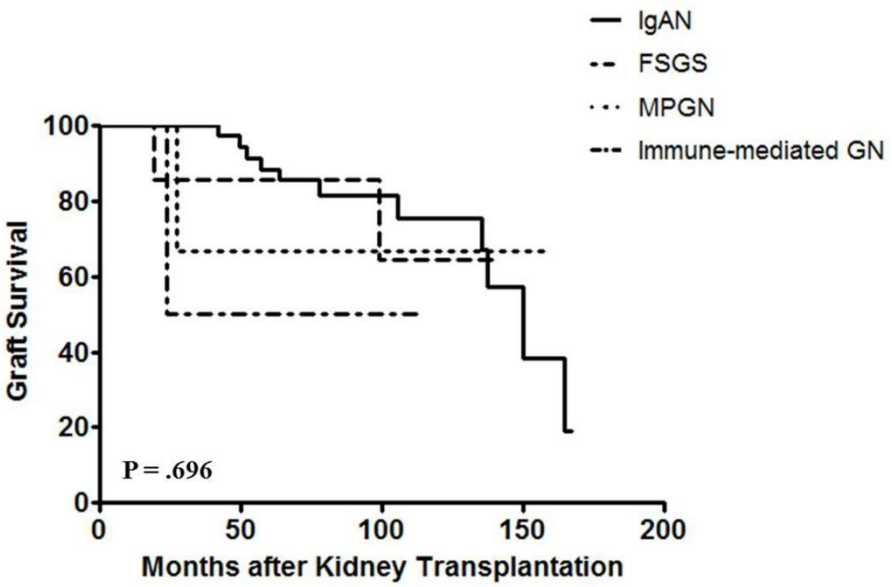


Figure 5. Effects on graft failure of the types of PTGN

There was no significant difference in graft survival between IgAN, FSGS, MPGN, and immune-mediated GN (P=0.696).

IgAN, immunoglobulin A nephropathy; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis

Risk factors for development of PTGN

Of the underlying kidney diseases, glomerular disease was a significant risk factor for PTGN (HR 3.63, 95% CI 1.73-7.65, p=0.001, Table 7, Figure 2). The incidence of PTGN increased in patients who had kidney transplantation since 2001, especially after 2006 (HR 2.52, 95% CI 1.16-5.46, p=0.019); however, after adjustment for other risk factors, this was not found to be statistically significant.

On the other hand, there was no difference in PTGN development according to age, gender, donor type, timing of referral, and preemptive transplantation. HLA mismatch was also not significantly associated with the development of PTGN.

The use of antimetabolites such as MMF and azathioprine did not influence PTGN development. The administration of basiliximab before transplantation and the use of tacrolimus actually increased the incidence of PTGN, and in multivariate analysis, these results were found to be statistically significant (HR 1.89, 95% CI 1.08-3.32, p=0.027) (HR 2.10, 95% CI 1.25-3.54, p=0.005) (Table 7, Figure 6, 7).

Table 7. Multiple risk factors for developing PTGN

	Univariate Analysis		Multivariate Analysis[1]	
	HR (95% CI)	**P**	**HR (95% CI)**	**P**
Underlying kidney disease				
Unknown	Reference		Reference	
Glomerular	3.63 (1.73 - 7.65)	.001	4.01 (1.82 - 8.84)	.001
Vascular	0.00	.953	0.00	.953
Interstitial/PN/Uropathy	0.83 (0.18 - 3.91)	.815	0.84 (0.17 - 4.04)	.826
Diabetic	1.63 (0.49 - 5.46)	.428	1.88 (0.54 - 6.53)	.320
Hereditary/Various	1.27 (0.38 - 4.23)	.695	1.23 (0.36 - 4.22)	.743
Era				
1995 - 2000	Reference			
2001 - 2005	1.76 (0.94 – 3.31)	.080		
2006 - 2010	2.52 (1.16 – 5.46)	.019		
HLA mismatch				
0	Reference			
1 - 3	0.86 (0.43 – 1.74)	.680		
4 – 6	1.04 (0.49 – 2.23)	.917		
Age at transplant (years)				
1st percentile	Reference			
2nd percentile	0.84 (0.46 - 1.53)	.566		
3rd percentile	0.60 (0.30 - 1.23)	.165		
4th percentile	0.82 (0.43 - 1.59)	.564		
Donor age (years)				
1st percentile	Reference			
2nd percentile	0.58 (0.31 - 1.09)	.090		
3rd percentile	0.62 (0.32 - 1.21)	.160		
4th percentile	0.62 (0.32 - 1.20)	.156		
Male Gender (Recipient)	0.74 (0.46 – 1.19)	.211		
Male Gender (Donor)	1.09 (0.67 – 1.75)	.734		
Donor type				
Living related	Reference			
Living unrelated	1.08 (0.57 – 2.05)	.823		

Deceased	1.25 (0.69 – 2.26)	.468		
Referral				
Late Referral	Reference			
Early Referral	0.84 (0.50 – 1.41)	.510		
Preemptive transplantation	0.59 (0.35 – 1.02)	.058		
Immunosuppressant				
Purine synthesis inhibitors				
Not use	Reference			
Azathioprine	0.49 (0.22 – 1.09)	.079		
Mycophenolate Mofetil	1.27 (0.65 – 2.47)	.489		
Calcineurin inhibitor				
Cyclosporine A	Reference		Reference	
Tacrolimus	2.26 (1.37 – 3.72)	.001	2.10 (1.25 - 3.54)	.005
Basiliximab	2.05 (1.20 – 3.52)	.009	1.89 (1.08 - 3.32)	.027

[1] Adjusted for following variables: underlying renal diseases, the era of transplantation, HLA mismatch, age and gender of recipient, preemptive transplantation, and administered immunosuppressants; DM, diabetes mellitus; HTN, hypertension; GN, glomerulonephritis; HLA, human leukocyte antigen; HR, hazard ratio

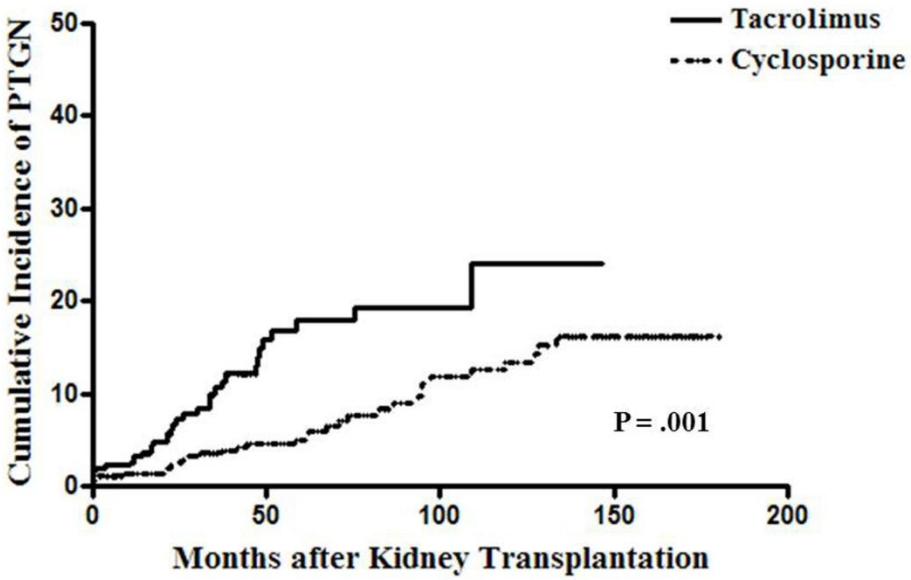


Figure 6. Association between PTGN and the use of calcineurin inhibitors

The use of tacrolimus increased the PTGN development compared with cyclosporine (P=0.001). PTGN, posttransplantation glomerulonephritis

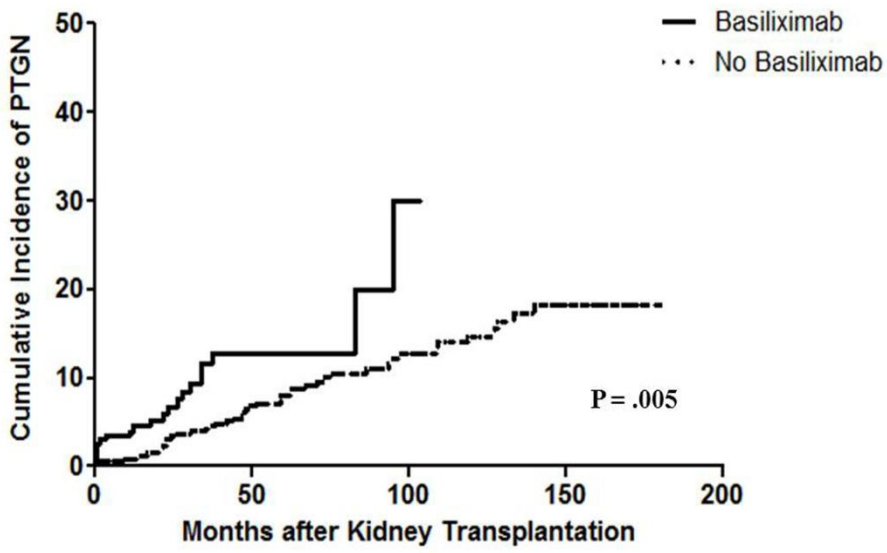


Figure 7. Association between PTGN and the use of basiliximab The use of basiliximab increased the PTGN development compared with no use of basiliximab (P=0.005). PTGN, posttransplantation glomerulonephritis

Discussion

The aim of this study was to analyze PTGN incidence, its relationship with allograft failure, and the risk factors for PTGN development. PTGN increased over the duration of follow up, reaching a cumulative probability of 17.0% after 10 years. The development of PTGN significantly decreased allograft survival. Among underlying kidney diseases, the highest occurrence of PTGN was in the glomerular diseases group; the most common type was IgAN. Also, we demonstrated that PTGN significantly contributed to allograft dysfunction, and eventual graft loss, regardless of the type of PTGN, and that PTGN incidence increased markedly in patients with baseline glomerular diseases and with the use of tacrolimus and basiliximab. We investigated patients' clinical courses and prognosis, including PTGN and allograft survival in the unknown etiology group. In many prior studies, these outcomes were analyzed only in patients with pathologically confirmed or presumed glomerular diseases.

The results of our study are consistent with those of earlier study, which reported that PTGN incidence among patients who underwent kidney transplantation after 2001 was significantly higher than prior to this, and that the risk for allograft failure was definitely increased in patients with PTGN (12). Chronic transplant glomerulopathy confirmed by pathologists were excluded from analysis of graft survival, therefore, we were able to verify the effect on allograft failure of only PTGN in this study.

PTGN developed steadily and consistently, and allograft loss due to PTGN increased throughout follow up, while the incidence of allograft loss due to acute rejection was the highest 1 year after transplantation, and decreased rapidly thereafter (13). This finding suggests that current immunosuppression regimens do not influence the incidence and course of PTGN, similar to the findings reported by Briganti et al (12, 13). In addition, our findings are confirmed by the presence of pathologically confirmed glomerular diseases in the native kidney as a critical predictor of PTGN (13). Additionally, this study verified the poorest graft survival in patients with both acute rejection and PTGN.

Moreover, the fact that administration of tacrolimus increased PTGN is confirmed by a prior study documenting that recipients treated with tacrolimus instead of CsA had more frequent proteinuria and an increased risk of graft failure (14). As proteinuria is a primary manifestation of GN, patients with PTGN have more proteinuria, interstitial change, and glomerular change, and eventually progress to allograft loss (15).

Among underlying glomerular diseases, FSGS was recurred at 5 out of 16 patients (31.3%), and MPGN and IgAN recurrence rate were 25.0% and 15.5%, respectively. These results were comparable with usual recurrence rates reported previously. On the other hands, MN was not recurred compared to the expected rate of 10 to 30%; it is supposed that this difference is due to demographic differences in study population of our centers, and that the recurrence rate will increase with longer follow-up duration (7).

In addition, our findings differ from those of Karakayali et al. in that

recurrence rates were similar among patients taking either tacrolimus or CsA (16) and from those of Gaston et al. in that recipients treated with tacrolimus had better kidney function than those on CsA-based treatment (17). Furthermore, the results of our study differ from another study that documented an increasing tendency towards PTGN development in living-related kidney transplants with a higher degree of HLA matching (18, 19).

Our study has a different level of significance compared to others, in that we demonstrated a positive correlation between the use of tacrolimus and basiliximab and PTGN. Even if better immunosuppression regimens decrease posttransplant complications, including treatment-resistant rejection and overall long-term mortality, prolonged graft survival and rejection free-survival was thought to contribute to the higher incidence of PTGN (20). In addition, completeness of follow up of the cohorts with administration of tacrolimus and basiliximab might influence this result.

After adjustment for multiple factors such as increased numbers of kidney biopsies, advances in medicine, and more accurate interpretations of pathologic results, our results appear to be meaningful. It is noteworthy that a cohort of three centers in Asia became the subject of this study and the duration of follow up was long enough to obtain an accurate interpretation of these results.

Also, even in underlying diabetic renal diseases, PTGN occurred to considerable extent accounting for 4.9%. It suggests that some patients with diabetes mellitus and renal failure may have underlying glomerular diseases, and therefore the patients without typical features and courses of diabetic

renal diseases need to be taken kidney biopsy to evaluate underlying glomerular diseases.

There were several limitations to our study. First, it was not possible to distinguish *de novo* glomerular diseases from recurrent glomerular diseases in a few patients, because pathologically unproven or only clinically diagnosed glomerular diseases were included in the underlying glomerular diseases group without clear criteria for classification, and 141 (18.5%) patients still remains to be unknown etiologies although underlying kidney diseases are classified into six groups detailedly. Also, some patients were categorized into original renal diseases without definite criteria. In other words, true incidence and influence of PTGN is under- or overestimated in this group. Thus, we need to design a follow up study with an accurate classification of *de novo* and recurrent GN. Second, allograft biopsies appeared to be performed more often in patients who underwent transplantation after 2001, regardless of the level of proteinuria (Supplement Table 1). This could have contributed to an exaggerated effect on the analysis of results. Accordingly, verification of the effects of tacrolimus and basiliximab should be practiced through well designed, multi-center, and prospective and the large cohort studies in the future.

It is expected that the number of kidney transplants will increase, and the development of effective immunosuppression will reduce early and late complications, and enhance comprehensive outcomes and survival after transplantation. In this light, the importance of PTGN will be emphasized. We demonstrated that PTGN has as prominent and considerable of an influence

on allograft survival as acute rejection, even in transplant recipients with ESRD of unknown etiology. We suggest that understanding the risk factors and prognosis of PTGN should play a significant role in monitoring and management of renal allograft patients in the future.

In conclusion, PTGN was strongly associated with the poor kidney allograft survival. A critical focus of posttransplant care should be the management of recurrent or *de novo* GN.

References

1. Choy BY, Chan TM, Lai KN. Recurrent glomerulonephritis after kidney transplantation. Am J Transplantv. 2006; 6(11): 2535-2542.

2. Golgert WA, Appel GB, Hariharan S. Recurrent glomerulonephritis after renal transplantation: an unsolved problem. Clin J Am Soc Nephrol. 2008; 3(3): 800-807.

3. Chadban S. Glomerulonephritis recurrence in the renal graft. J Am Soc Nephrol. 2001; 12(2): 394-402.

4. Hariharan S. Long-term kidney transplant survival. Am J Kidney Dis. 2001; 38(6 Suppl 6): S44-S50.

5. Hariharan S, Adams MB, Brennan DC, Davis CL, First MR, Johnson CP, et al. Recurrent and de novo glomerular disease after renal transplantation: a report from Renal Allograft Disease Registry (RADR). Transplantation. 1999; 68(5): 635-641.

6. Denton MD, Singh AK. Recurrent and de novo glomerulonephritis in the renal allograft. Semin Nephrol. 2000; 20(2): 164-175.

7. O'Meara Y, Green A, Carmody M, Donohoe J, Campbell E, Browne O, et al. Recurrent glomerulonephritis in renal transplants: fourteen years' experience. Nephrol Dial Transplant. 1989; 4(8): 730-734.

8. Han SS, Huh W, Park SK, Ahn C, Han JS, Kim S, et al. Impact of recurrent disease and chronic allograft nephropathy on the long-term allograft outcome in patients with IgA nephropathy. Transpl Int. 2010; 23(2): 169-175.

9. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ,

Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. N Engl J Med. 2000; 342(9): 605-612.

10. Ostrowska J, Pazik J, Lewandowski Z, Mroz A, Perkowska-Ptasinska A, et al. Posttransplantation glomerulonephritis: risk factors associated with kidney allograft loss. Transplant Proc. 2007; 39(9): 2751-2753.

11. Briggs JD, Jones E. Recurrence of glomerulonephritis following renal transplantation. Scientific Advisory Board of the ERA-EDTA Registry. European Renal Association-European Dialysis and Transplant Association. Nephrol Dial Transplant. 1999; 14(3): 564-565.

12. Chailimpamontree W, Dmitrienko S, Li G, Balshaw R, Magil A, Shapiro RJ, et al. Probability, predictors, and prognosis of posttransplantation glomerulonephritis. J Am Soc Nephrol. 2009; 20(4): 843-851.

13. Briganti EM, Russ GR, McNeil JJ, Atkins RC, Chadban SJ. Risk of renal allograft loss from recurrent glomerulonephritis. N Engl J Med. 2002; 347(2): 103-109.

14. Sancho A, Gavela E, Avila A, Morales A, Fernandez-Najera JE, Crespo JF, et al. Risk factors and prognosis for proteinuria in renal transplant recipients. Transplant Proc. 2007; 39(7): 2145-2147.

15. Couser W. Recurrent glomerulonephritis in the renal allograft: an update of selected areas. Exp Clin Transplant. 2005; 3(1): 283-288.

16. Karakayali FY, Ozdemir H, Kivrakdal S, Colak T, Emiroglu R, Haberal M. Recurrent glomerular diseases after renal transplantation. Transplant Proc. 2006; 38(2): 470-472.

17. Gaston RS. Current and evolving immunosuppressive regimens in

kidney transplantation. Am J Kidney Dis. 2006; 47(4 Suppl 2): S3-S21.

18. Mathew TH. Recurrence of disease following renal transplantation. Am J Kidney Dis. 1988; 12(2): 85-96.

19. Andresdottir MB, Hoitsma AJ, Assmann KJ, Koene RA, Wetzels JF. The impact of recurrent glomerulonephritis on graft survival in recipients of human histocompatibility leucocyte antigen-identical living related donor grafts. Transplantation. 1995*;* 68(5): 623-627.

20. Yang H. Maintenance immunosuppression regimens: conversion, minimization, withdrawal, and avoidance. Am J Kidney Dis. 2006; 47(4 Suppl 2): S37-S51.

초 록

서론: 이식 후 사구체신염 (posttransplant glomerulonephritis)은 이식 신 상실의 중요한 원인으로, 그 중요성이 최근 재조명되고 있다. 본 연구의 목적은 이식 후 사구체신염의 발생률을 확인하고, 이와 이식 신 상실과의 연관성을 파악하며, 이식 후 사구체신염의 위험인자들을 분석하는 것이다.

방법: 1995년부터 2010년까지 다기관 코호트에서 신장 이식을 받은 996명의 환자들 중, 764명의 환자들을 대상으로 연구를 진행하였다.

결과: 이식 후 사구체신염은 이식 후 5년째와 10년째에 각각 9.7%와 17.0%의 발생률을 보였다. 조직검사로 입증 되었거나 임상적으로 진단받은 사구체 질환 환자들 중, 17.8%에서 이식 후 사구체신염이 발생하였으며, 신 혈관 질환, 간질성 신 질환/신우신염/요로질환, 당뇨병성 신 질환, 유전성 신 질환, 그리고 원인 불명의 신 질환을 진단받은 환자들에서는 각각 0%, 4.4%, 4.9%, 5.5%, 그리고

5.7%에서 이식 후 사구체신염이 발생하였다. 이식 후 사구체신염이 발생한 환자에서 이식신의 생존은 유의하게 감소하였다. 이는 이식신 상실을 4배 가량 증가시켰으며, 급성 거부반응과 동시에 발생한 경우에는 약 7배 증가하는 결과를 보였다. 이식 후 사구체신염의 위험인자를 분석한 결과, 다른 위험인자들을 보정한 후에도, 기저에 사구체 질환을 진단받은 경우와 tacrolimus와 basiliximab을 사용한 경우에 이식 후 사구체신염이 유의하게 증가하는 것을 확인할 수 있었다.

결론: 이식 후 사구체신염은 이식신의 불량한 예후와 밀접하게 연관되어 있다. 따라서, 신장 이식 후에 재발성 혹은 *de novo* 사구체신염의 발생에 적절하게 대처하는 것이 중요하겠다.

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주요어: 신장 이식, 사구체신염, 위험인자, 이식신 생존
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