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主論文

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Clinical and Pathological Features of Plasma Cell-Rich Acute Rejection after Kidney Transplantation

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Authors' contributions

JH and KH participated in study design; JH, HS, KO, MO, SF and MH participated in collecting the data; JH, KH and MO participated in the data analysis and interpretation; JH, KH and MO participated in statistical analysis; JH, KH, KO and MO participated in writing the manuscript; SW, HS, HI, SF, MH and KT participated in the performance of the study and provided significant intellectual input.

Disclosure

All authors have no conflicts of interests.

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Abbreviation

Abbreviations: ABMR, antibody-mediated rejection; ATG, anti-thymoglobulin; CI, confidence intervals; DSA, donor-specific antibody; HR, Hazard ratio; IQR, interquartile range; PCAR, plasma cell-rich acute rejection; PAS, periodic acid–schiff; PAM, periodic acid-methenamine-silver; PTLD, posttransplantation lymphoproliferative disorder; SD, standard division; TCMR, T-cell–mediated rejection; TLO, tertiary lymphoid organ

Abstract

Background Plasma cell-rich acute rejection (PCAR) is a rare type of allograft rejection characterized by the presence of mature plasma cells. In general the prognosis of PCAR is poor, and its clinical and pathological features remain unclear.

Methods We performed a retrospective observational study and compared allograft survival between kidney transplant recipients who developed PCAR and those who did not develop PCAR. We further analyzed clinical and pathological risk factors for allograft failure in PCAR patients.

Results Of 1,956 recipients, 40 developed PCAR. There was a higher prevalence of deceased donor transplants (27.5% vs. 11.7%, P=0.0059), longer median total ischemia time (99 min, interquartile range: 71 – 144, vs. 77 min, interquartile range: 59 – 111, P=0.0309), and lower prevalence of ABO-incompatible transplantation (7.5% vs. 22.5%, P=0.0206) in patients with PCAR than in those without PCAR.

Multivariate Cox regression analysis showed that development of PCAR was associated with

allograft loss (Hazard Ratio=8.03, 95% Confidence Interval: 3.89 – 14.80, P<0.0001).

We classified PCAR according to the Banff 2015 criteria into a borderline change group, a T-cell–mediated rejection (TCMR) group, an antibody-mediated rejection (ABMR) or suspected of having ABMR (ABMR/sABMR) group, and a mixed rejection (TCMR/ABMR) group. The ABMR/sABMR group was associated with a lower rate of allograft survival without significant difference (log-rank test P=0.1692).

Conclusions The results indicated that PCAR was an independent risk factor for allograft loss. PCAR presented with all types of rejection in the Banff 2015 criteria, and ABMR/sABMR was associated with poor allograft survival.

Keywords: antibody-mediated rejection, donor-specific antibody, kidney transplantation, plasma cell-rich acute rejection

Introduction

Plasma cell-rich acute rejection (PCAR) is a rare type of allograft rejection characterized by infiltration of mature plasma cells. Since the first report by David-Neto et al in 1993,[1] this type of rejection has been described in some studies and case reports and is now characterized by poor graft survival and refractoriness to treatment,[2,3] In general the prognosis of PCAR is poor, and its clinical and pathological features remain unclear. In addition, our understanding of allograft rejection has improved, and we now categorize T-cell-mediated rejection (TCMR) and antibody-mediated rejection (ABMR) according to the latest Banff 2015 criteria.[4] PCAR has been described as either Banff IA or IB (TCMR),[5] but we recently reviewed some PCAR cases with histological features of ABMR or mixed TCMR/ABMR, with serological evidence of donor-specific antibody (DSA).[6]

To clarify the pathogenesis and etiology of PCAR, we investigated clinical and pathological characteristics.

Methods

Patient and study setting

This was a retrospective observational study. We assessed 1,956 kidney transplantation procedures and 9,347 kidney allograft biopsies performed between 1999 and 2012 at our institution and related hospitals. The samples were collected in the Department of Pathology in our institution and diagnosed by experienced pathologists. The primary outcome was death-censored graft survival (defined as the date of initiation of either form of renal replacement therapy after first indication biopsy).

The patients were divided into a PCAR group and a non-PCAR group. The inclusion criteria for PCAR were diagnosis of allograft rejection according to the Banff 2015 classification[4] and the presence of more than 10% plasma cells among all infiltrating cells in the cortex, counted in 10 serial, high-power fields using periodic acid–Schiff (PAS), periodic acid-methenamine-silver (PAM), and/or hematoxylin and eosin staining (Figure 1). As described previously,[2] plasma cells were easily identifiable by their "clock-face" nuclear chromatin, eccentric nuclei, amphophilic/eosinophilic cytoplasm, and paranuclear pale zone. We confirmed these cells were stained by CD138 in some cases.

We excluded cases that were diagnosed with reflux nephropathy or pyelonephritis, or were biopsied after the induction of dialysis, or showed adenovirus or polyomavirus nephropathy using hematoxylin and eosin-based identification of viral inclusions[7] and simian virus 40 immunohistochemistry (mouse monoclonal antibody, diluted 1:600, PAb416; Abcam plc, Cambridge, UK). Samples showing posttransplantation lymphoproliferative disorder (PTLD) nephropathy were also excluded by in situ hybridization for Epstein-Barr virus-encoded RNA and plasma cell monoclonality, as verified by immunostaining of immunoglobulin heavy chains (IgG, IgA, IgM) and light chains (kappa and lambda), when in situ hybridization for Epstein-Barr virus-encoded RNA was positive.

The procedures followed were in accordance with the Declaration of Helsinki and its revisions. This study was reviewed and approved by the local institutional review board (approval number 3506).

Banff classification

All biopsies that met the above criteria were diagnosed with PCAR and classified by experienced pathologists using the Banff 2015 criteria.[4] C4d staining was performed via immunohistochemistry on deparaffinized sections, as previously described,[8,9] and interpreted

according to the recommendations of the Banff criteria.

We classified all biopsies of PCAR into 4 rejection types (borderline change, TCMR, ABMR, and mixed TCMR/ABMR).[4] In brief, borderline changes were diagnosed in cases with foci of tubulitis (t1, t2, or t3) with minor interstitial inflammation (i0 or i1), or interstitial inflammation (i1, i2, i3) with mild tubulitis (t1). TCMR was diagnosed in cases with histological evidence of both significant interstitial inflammation (Banff interstitial inflammation score, $i \geq 2$) and moderate to severe tubulitis (Banff tubular inflammation score, $t \geq 2$). ABMR was diagnosed in cases with histological evidence of microvascular inflammation (Banff glomerular inflammation score, $g \geq 1$ and/or Banff peritubular capillary inflammation score, $ptc \geq 1$), with linear C4d staining in peritubular capillaries (Banff C4d score, $c4d \geq 2$), or moderate microvascular inflammation ($g+ptc \geq 2$) without linear C4d staining in peritubular capillaries ($c4d \leq 1$). In this report, we suspected ABMR (sABMR) if the cases showed pathological features but did not show serologic evidence of DSA or if DSA status was unknown. Mixed TCMR/ABMR was diagnosed in cases with histological evidence of both TCMR and ABMR or sABMR.

Clinical data

The clinical data of patients in the present study were collected from their hospital records.

The regimen or dose of immunosuppression was changed by the primary clinician according to clinical status and the presence of infection (viral or bacterial), uncontrolled side effects, or pregnancy. We screened for polyomavirus nephropathy according to guidelines.[10] We monitored urinary cytology every month; if decoy cells were present, we tested urine and/or blood for BK viral load and considered allograft biopsy.

Donor-specific antibodies

Patients were evaluated for HLA sensitization status using a complement-dependent cytotoxicity assay. Serum samples were examined for IgG antibody against HLA class I or II, using Flow PRA or LABScreen Mixed (One Lambda, Canoga Park, CA, USA). DSA was identified on screening of HLA antibody-positive recipients using LABScreen single antigen beads (One Lambda). Mean fluorescent intensity values over 1,000 were determined to be positive.

Data analysis

All analyses were performed using the JMP software package (ver. 10.0.0; SAS Institute). Data were summarized as means ± standard division (SD), median and interquartile range (IQR), or frequencies. Categorical variables were analyzed with the chi-squared test, Fisher's exact test,

and the 2–group proportion test, whereas continuous variables were compared by using the paired t-test, the Wilcoxon signed-rank test, the Mann-Whitney U test, the Kruskal-Wallis H test, or analysis of variance, as appropriate. Kaplan-Meier curves and log-rank tests were used to compare death-censored allograft survival rates. The Cox proportional-hazards model was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for death-censored allograft survival. All P-values were 2-sided, and P-values of 0.05 were considered to indicate statistical significance.

Results

Population and criteria

Between 1999 and 2012, 1,956 kidney transplantations and 9,347 kidney biopsies were performed (Figure 2). Fifty biopsy samples from 50 allografts matched the inclusion criteria and were diagnosed with plasma cell-rich infiltration; 10 cases were excluded (4 cases of reflux nephropathy, 3 cases of BK virus nephropathy, 1 case of PTLD in the allograft, 1 case of drug-induced nephropathy, and 1 case in which biopsy was performed after initiation of hemodialysis). Forty biopsy samples from 40 patients were diagnosed with PCAR and the other 1,916 patients were defined as non-PCAR patients. The prevalence of PCAR was 2.0% of all allografts.

Clinical demographics of PCAR and non-PCAR patients

The baseline characteristics of the patients at kidney transplantation are shown in Table 1. There was no significant difference between the PCAR and non-PCAR patients in terms of age, sex, primary kidney disease, donor status, warm ischemia time, prior history of transplantation, HLA mismatch, positive prevalence of cross-matching, or induction or maintenance immunosuppression regimen. The prevalence of deceased donor transplants was higher in PCAR patients (27.5%) than in non-PCAR patients (11.7%, P=0.0059). The median total ischemia time was longer in PCAR patients (99 min, IQR: 71 – 144) than in non-PCAR patients (77 min, IQR: 59 – 111, P=0.0309). The prevalence of ABO-incompatible transplantation was lower in PCAR patients (7.5%) than in non-PCAR patients (22.5%, P=0.0206).

Clinical outcome of PCAR and non-PCAR patients

Allograft survival in patients with and without PCAR is shown in Figure 3. PCAR patients showed significantly lower death-censored allograft survival than in non-PCAR patients, according to the Kaplan-Meier analysis (log-rank test P<0.0001).

Multivariate Cox regression analysis was performed to identify risk factors for allograft loss (Table 2). Development of PCAR was associated with allograft loss (HR=8.03, 95% CI: 3.89 – 14.80, P<0.0001), as was deceased donor transplantation (HR=1.99, 95% CI: 1.20 – 3.20,

P=0.0086).

Onset time of PCAR

The onset time of PCAR is shown in Figure 4. PCAR developed in the early period after transplantation; the number of cases increased after 1 year and then began to slow. The median time to rejection onset was 605 days (1.6 years), with a range of 21 days to 18.8 years after transplantation.

Clinical characteristics of PCAR patients according to the Banff 2015 criteria

We divided 40 cases of PCAR into 4 types: 4 were in the borderline change group, 14 in the TCMR group, 9 in the ABMR/sABMR group, and 13 in the mixed-type rejection (TCMR/ABMR) group. The clinical characteristics of each type are shown in Table 3. There were no significant differences between the groups in age, sex, ABO-incompatible transplantation, prevalence of DSA, and serum creatinine at baseline or at biopsy. A prior history of biopsy-proven rejection was noted in 9 of the 40 PCAR patients, with a higher rate in those with ABMR/sABMR (44.4%) than in other types; this was not statistically significant (P=0.2218). In addition to rejection, interstitial fibrosis/tubular atrophy was diagnosed in 2 cases, recurrence of IgA nephropathy in 2 cases, and recurrence of focal segmental glomerulosclerosis

in 1 case prior to PCAR onset. Duration from transplantation to onset of PCAR was longer in the ABMR/sABMR group (median: 1,384 days, IQR; 643 – 3,162) than in other groups, without statistical significance (P=0.0807).

Of the 40 PCAR patients, 35 received treatment for rejection. There were no differences in steroid (either oral or intravenous) or anti-T-cell treatment (including gusperimus, anti-thymoglobulin, and muromonab-CD3) between the PCAR types. Anti-B-cell treatment (including rituximab, plasma exchange, and intravenous immunoglobulin) was used significantly more in the TCMR/ABMR groups (84.6%) than in other groups (P=0.0092).

Pathologic characteristics of PCAR patients according to the Banff 2015 criteria

The pathological characteristics of each type are shown in Table 4. Interstitial inflammation scores (i) and tubulitis scores (t) were significantly higher in borderline change, TCMR, and TCMR/ABMR groups than in the ABMR/sABMR group. Glomerulitis scores (g), peritubular capillaritis scores (ptc), and C4d staining scores (c4d) were significantly higher in the ABMR/sABMR and TCMR/ABMR groups than in the borderline change and TCMR groups. Chronic glomerulopathy (cg), arteriolar hyalinosis (ah), hyaline arteriolar thickening (aah), interstitial fibrosis (ci), and tubular atrophy scores (ct) were significantly higher in the

ABMR/sABMR group than in the other groups. There were no differences in vasculitis (v) or vascular fibrous intimal thickening scores (cv) between the groups.

Seven cases had tertiary lymphoid organs (TLOs) in the cortical interstitial area, but there was no difference in prevalence between the groups (P=0.4254).

Allograft survival in PCAR patients according to the Banff 2015 criteria

Allograft survival in PCAR patients according to the Banff 2015 criteria is shown in Table 4 and Figure 5. Among all PCAR cases, the 1-year allograft survival was 86.4% and the median allograft survival time was 2,478 days. According to classification, the median allograft survival time in the borderline change and TCMR groups was longer than the observation time. The ABMR group had a shorter median allograft survival time than the other groups, without a significant difference (P=0.1661). Kaplan-Meier analysis showed that patients in the ABMR/sABMR group had a lower rate of allograft survival than other groups, without a significant difference (log-rank test P=0.1692).

Multivariable Cox regression analysis was performed to identify risk factors associated with allograft survival other than those in the Banff 2015 classification, as shown in Table 5. The

analysis showed that serum creatinine level at biopsy was associated with allograft loss (HR=1.87, 95% CI: 1.07 – 3.35, P=0.0274). Recipient age, biopsy time since transplantation, and detection of DSA were not independently associated with allograft loss.

Discussion

The etiology of plasma cell infiltration in allografts is not well-understood. In settings of allograft organ transplantation, B cells receive activating signals by binding with antigens and activated by interacting with CD4+ T cells in germinal center, and finally differentiate into plasma cells or memory B cells.[11] Some plasma cells migrate into bone marrow and live long, but usually they did not infiltrate in allograft organs.

Previous clinical observational studies indicated that infiltration of plasma cells in allografts was associated with drug hypersensitivity, infection,[1] or PTLD nephropathy.[2] Moreover, reflux nephropathy and BKV nephropathy cases also showed plasma cell infiltration in our cohort. After we excluded these, the remaining cases were considered "plasma cell-rich acute rejection (PCAR)," as reported by Charney et al.[5] The possibility that these excluded cases were falsely considered PCAR should be noted.

Risk factors for developing PCAR have been considered. Among baseline characteristics in our study, deceased donor transplantation, longer total ischemia time, and non-ABO incompatible transplantation were more frequent in PCAR patients than in non-PCAR patients. Longer duration from transplantation to rejection onset,[12] tapering or withdrawal of immunosuppression,[13] and nonadherence to immunosuppression[14,15] were also reported to be associated with PCAR. Our cohort included 4 cases of chronic immunosuppression underdosing, and 9 cases of change in immunosuppression regimen prior to PCAR. We also found recurrent IgA nephropathy in 2 cases, and recurrent focal segmental glomerulosclerosis in 1 case, but could not confirm their association with PCAR.

PCAR showed all histological types of rejection according to the Banff 2015 criteria. Among the 40 PCAR patients, the ABMR/sABMR group showed the worst allograft survival. The ABMR/sABMR type was associated with longer duration from transplantation to rejection onset, greater prior history of acute rejection, greater prevalence of DSA, and higher ci and ct scores. These factors might result in a worse outcome. We also examined the prevalence of TLOs, which often develop at sites of transplant allografts and are considered germinal center reactions, resulting in anti-HLA-producing plasma cells and memory B cells.[16] TLOs have also reportedly been associated with allograft tolerance,[17,18] but showed no association with allograft survival in

our study.

Among our PCAR cases, 3 had intimal arteritis. Wu et al reported that intimal arteritis could be found in all types of rejection, and that intimal arteritis associated with ABMR had worse outcomes.[19] However, we did not find an association between intimal arteritis (v score) and PCAR cases.

The prognosis of PCAR was poor in our study. The development of PCAR was a risk factor for allograft loss regardless of background status (HR=8.03, 95% CI: 3.89 – 14.80, P<0.0001). Meehan et al[2] reported a 1-year allograft survival rate in PCAR of 56%, and Desvaux et al[3] reported a 40% rate among those refractory to immunosuppression therapy. The reason for better allograft survival in our study was not clear, but it is possible that the exclusion criteria were different and that more intensive treatment in our study improved the prognosis of PCAR.

Allograft survival differed from that reported in the Banff classification and the ABMR/sABMR group showed the worst prognosis, without a statistical difference (log-rank test, P=0.1692). Abbas et al[20] reported that 64% of PCAR cases had detectable DSA and cases with DSA had worse allograft survival. Detectable DSA was not an independent risk factor for allograft loss in

our cohort, but DSA at the time of rejection was only assessed in 60% of cases. The onset time of acute rejection has been reported to affect the clinical outcome, regardless of the Banff classification,[21] but late onset was not an independent risk factor for allograft failure in our cohort.

Various treatment regimens were used for PCAR because this was a retrospective cohort study. Most of the cases were treated with more than 1 therapy. Many physicians chose therapies on the basis of the clinical and histological findings in each case, depending on the presence of DSA or the Banff classification score.

There were several limitations. This was a single-center, retrospective study, the sample size (N = 40) was small, the PCAR definition has not been confirmed, the treatments differed in each case, and DSA at the time of rejection was assessed in only 60% of cases.

In conclusion, PCAR was an independent risk factor for allograft loss. PCAR showed all types of rejection according to the Banff 2015 classification, and the ABMR/sABMR-group was associated with poor allograft survival.

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Figure legend

Figure 1 Histological findings of PCAR in kidney allografts

Upper Left; Tubulointerstitial rejection with diffuse inflammatory infiltrates (PAS, x200). Upper Right; A magnified view of interstitial and tubular inflammation demonstrating plasma cells, lymphocytes, and some eosinophils (PAM, x400). Lower Left; Infiltrated plasma cells (CD 138 staining, x400).

Figure 2 The flow criteria of PCAR patients through the study

A total of 9347 kidney biopsies of 1956 allograft kidneys were evaluated. Fifty biopsy samples matched the inclusion criteria and 10 cases were excluded. Forty biopsies were diagnosed with PCAR.

Figure 3 Graft survivals of PCAR and non-PCAR patients

The Kaplan–Meier curves showed death-censored allograft survival time after kidney transplantation of patients with PCAR or without PCAR (non-PCAR).

Figure 4 The cumulative incidence of PCAR

The cumulative incidence of PCAR showed PCAR onset period from transplantation.

Figure 5 Graft survival of PCAR among rejection types in Banff classification

The Kaplan–Meier curves showed death-censored allograft survival time after biopsy of patients in each group.

Figure 1

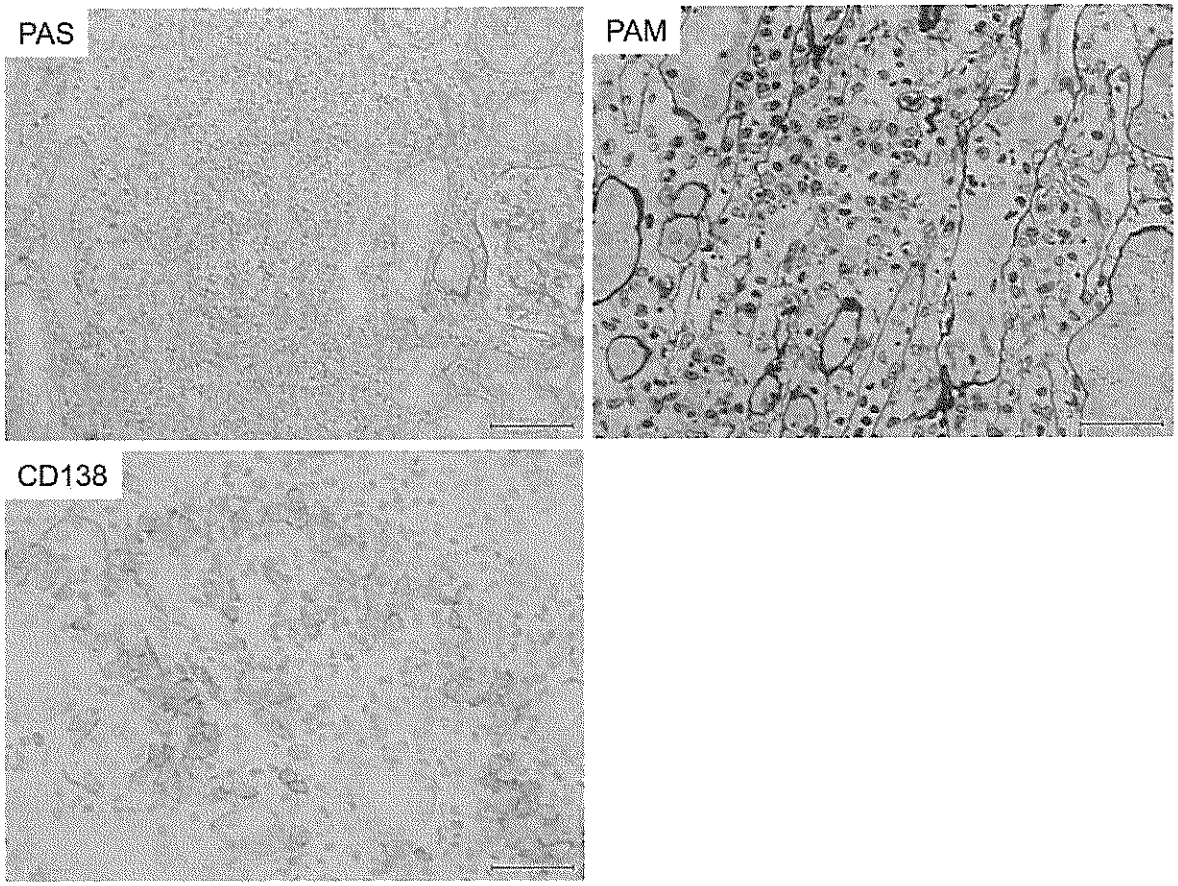

Figure 2

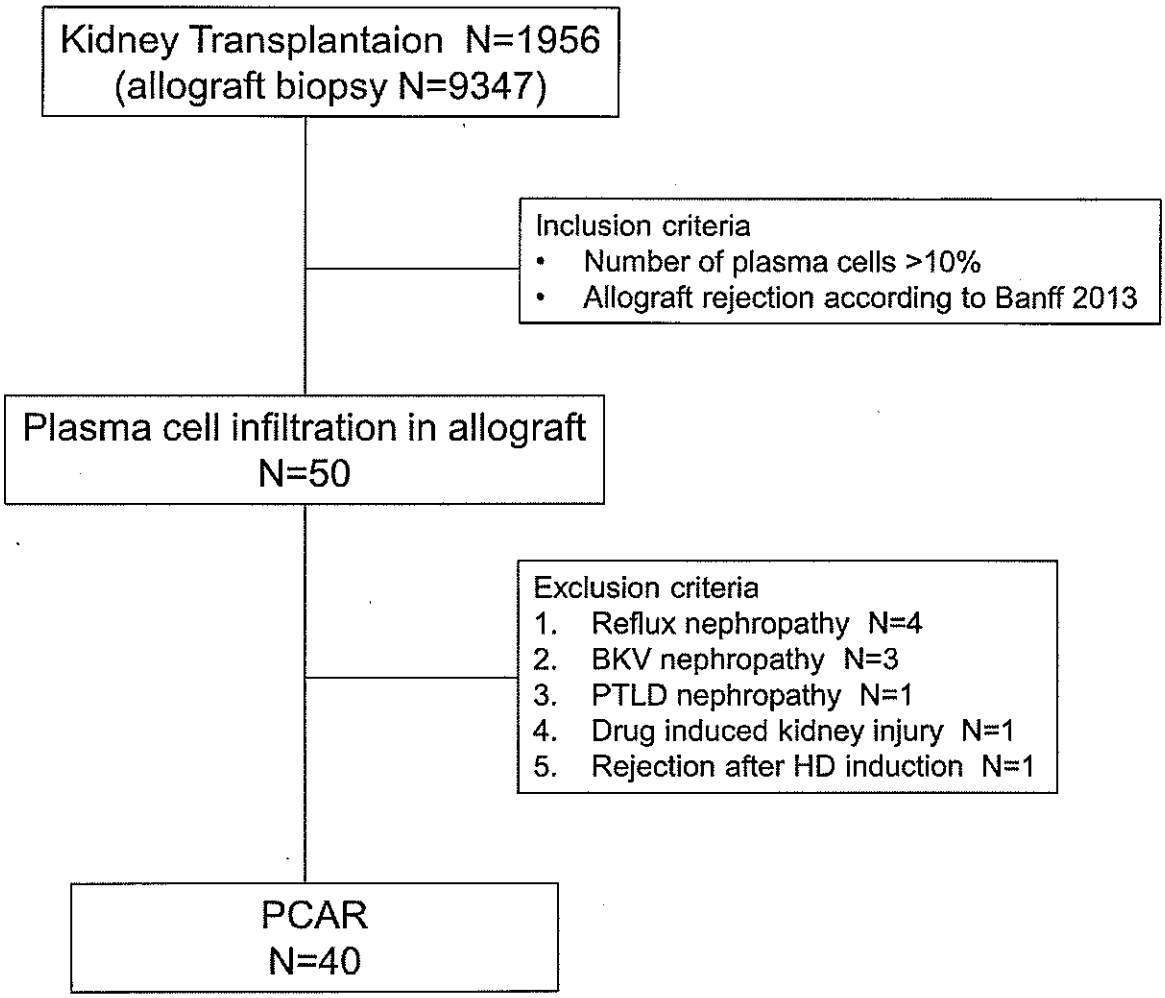

Figure 3

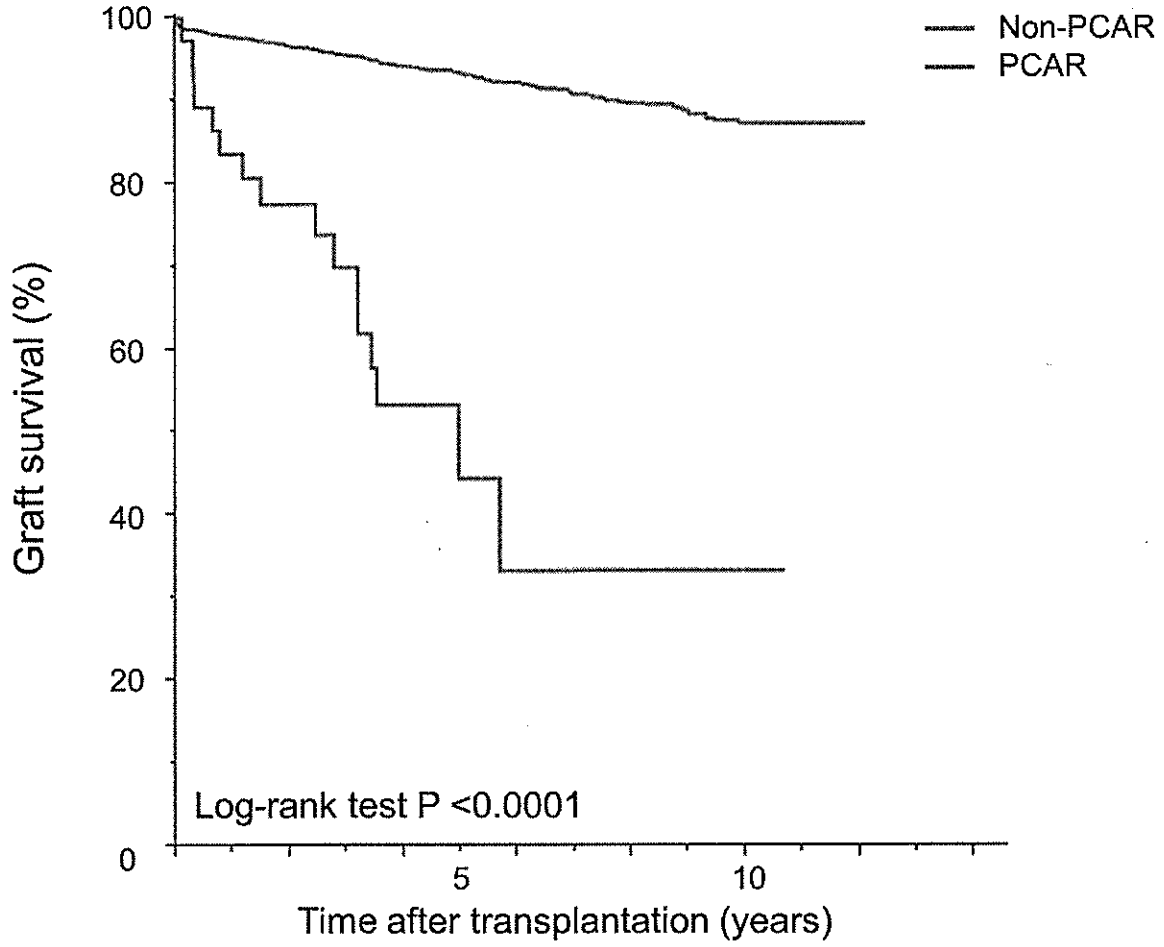

Figure 4

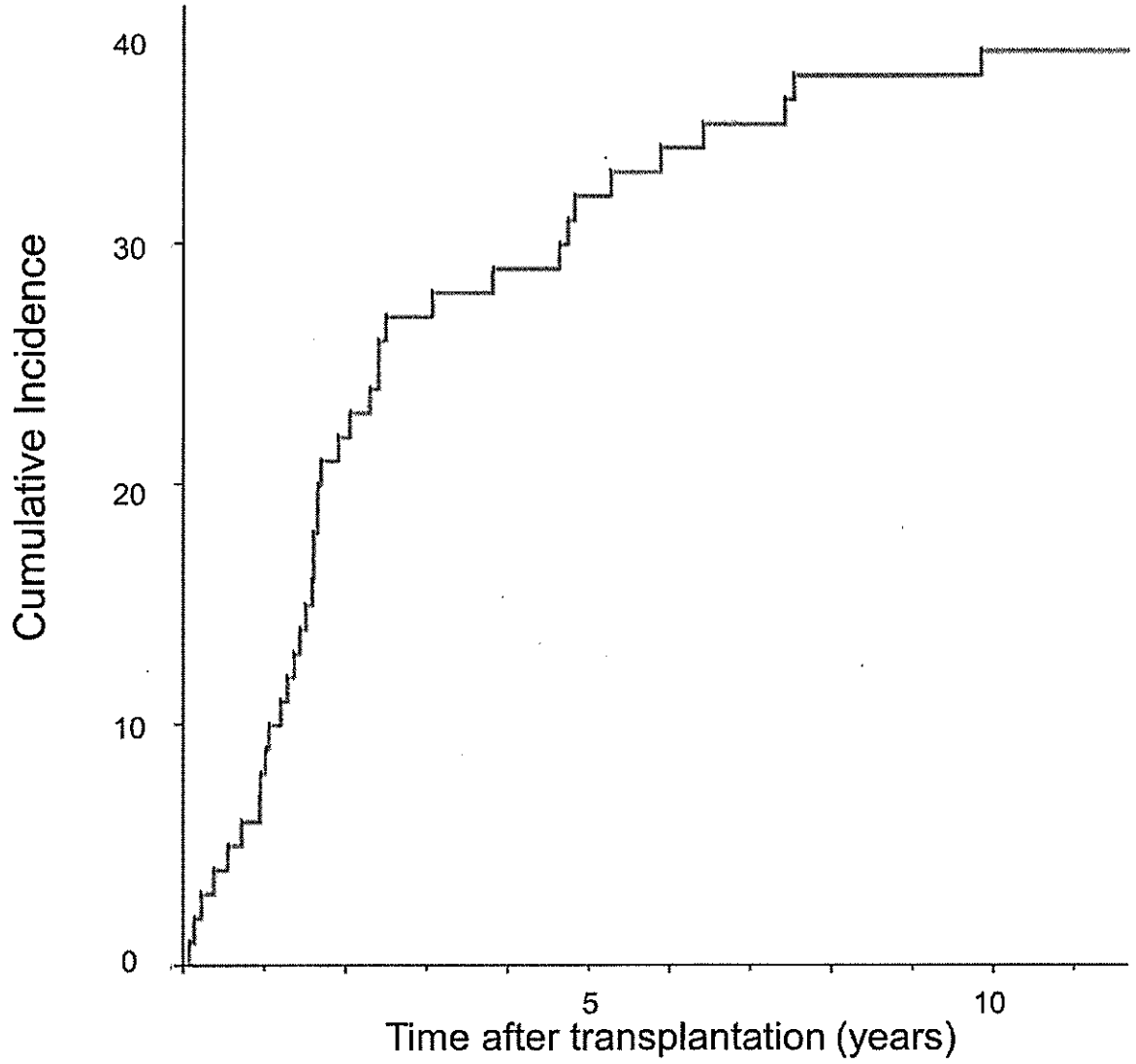

Figure 5

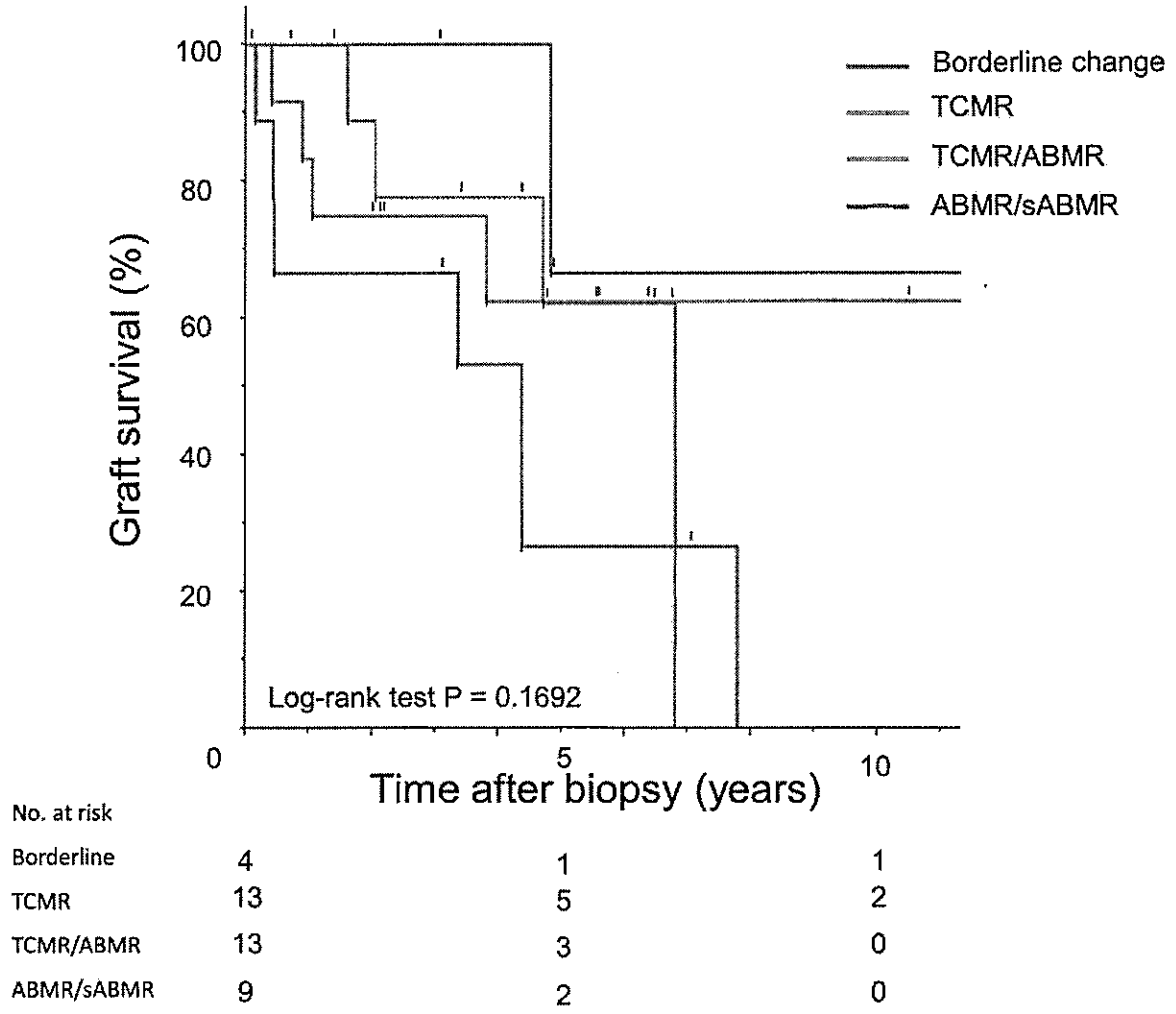

Table 1 Demographic and clinical characteristics

	PCAR (N=40)	Non-PCAR (N=1916)	P-value
Age, years, mean ± SD	41.7 ± 14.4	42.0 ± 16.0	0.8813
Male, N (%)	21 (52.5)	1177 (61.4)	0.2555
Primary disease, N (%)			
Glomerulonephritis	13 (32.5)	499 (27.0)	0.4721
Diabetes Mellitus	8 (20.0)	245 (12.8)	0.2279
Nephrosclerosis	2 (5.0)	59 (3.1)	0.3566
Others (including unknown)	17 (42.5)	655 (34.2)	0.3129
Donor age, years, mean ± SD	54.6 ± 11.5	54.5 ± 11.8	0.9676
Donor sex, male, N (%)	8 (42.1)	747 (39.0)	0.8157
Deceased donor, N (%)	11 (27.5)	225 (11.7)	0.0059
Warm ischemia time, min, median (IQR)	4 (3-5)	4 (3-5)	0.8486
Total ischemia time, min, median (IQR)	99 (71-144)	77 (59-111)	0.0309
Pre transplantataion, N (%)	3 (7.5)	134 (7.0)	0.7569
ABO-incompatible transplantation, N (%)	3 (7.5)	431 (22.5)	0.0206
HLA-mismatch, N, median (IQR)			
Class-I	2 (1-2)	2 (1-2)	0.5618
Class-II	1 (1-1)	1 (0-1)	0.7928
Cross matching, N (%)			
T cell	0 (0)	2 (0.12)	1.0000
B cell	2 (7.1)	46 (2.76)	0.1873

Immunosuppression treatment			
Basiliximab	30 (75.0)	1396 (73.2)	1.0000
Rituximab	11 (27.5)	557 (29.2)	1.0000
Splenectomy	3 (7.5)	186 (9.7)	1.0000
Tacrolimus	24 (60.0)	1175 (61.4)	0.8707
Cyclosporine	16 (40.0)	737 (38.5)	0.8705
Azathioprine	4 (10.0)	81 (4.2)	0.0927
Mizoribine	2 (5.0)	116 (6.1)	1.0000
Mycophenolate mofetil	32 (80.0)	1662 (86.8)	0.2355
Evelolimus	2 (5.0)	48 (2.5)	0.2728

Table 2 Risk factor of allograft loss according to Cox regression analysis

	HR	95% CI	P-value
PCAR (vs non-PCAR)	8.03	3.89 – 14.80	<0.0001
Age (per year)	0.99	0.98 – 1.00	0.2086
Male	1.30	0.94 – 1.83	0.1136
Diabetes Mellitus as primary disease	1.33	0.80 – 2.10	0.2642
ABO-incompatible	1.40	0.94 – 2.04	0.0949
Deceased donor	1.99	1.20 – 3.20	0.0086
Pretransplantation	1.28	0.68 – 2.18	0.4198
HLA class I mismatch ≥1	1.45	0.78 – 3.00	0.2506
HLA class II mismatch ≥1	1.42	0.94 – 2.20	0.0949
Cross match positive	0.35	0.02 – 1.68	0.2116

Table 3 Demographic and clinical characteristics of PCAR among rejection types of Banff 2015 classification

Category	Borderline (N=4)	TCMR (N=14)	ABMR /sABMR (N=9)	TCMR/ABMR (N=13)	P-value
Age, years, mean ± SD	41.0 ± 17.9	43.2± 12.7	41.8 ± 17.4	40.1 ± 14.7	0.9587
Male, N (%)	1 (25.0)	6 (42.9)	4 (44.4)	10 (76.9)	0.1661
ABO incompatible, N (%)	1 (25.0)	1 (7.1)	0 (0)	1 (7.7)	0.4755
Prior rejection, N (%)	1 (25.0)	1 (7.1)	4 (44.4)	3 (23.1)	0.2218
Time to biopsy after transplant, days, median (IQR)	489 (147-4815)	580 (179-880)	1384 (643-3162)	611 (404-1834)	0.0807
Serum Cr at baseline, mg/dL, mean ± SD	1.09 ± 0.38	1.28 ± 0.39	1.55 ± 0.70	1.25 ± 0.31	0.3370
Serum Cr at biopsy, mg/dL, mean ± SD	1.43 ± 0.62	2.60 ± 1.41	2.68 ± 0.96	2.83 ± 1.39	0.2923
DSA at diagnosis, N (%)	0 (0)	0 (0)	0 (0)	2 (15.4)	0.3330
Preexisting DSA	1 (25.0)	2 (14.3)	2 (22.2)	2 (15.4)	0.3102
De-novo DSA	3 (75.0)	5 (35.7)	5 (55.6)	4 (30.8)	0.3404
No data					
Treatment, N (%)					
Steroid	0 (0)	4 (28.6)	1 (11.1)	1 (7.7)	0.3367
Anti-T cell	3 (75.0)	6 (42.9)	3 (33.3)	9 (69.2)	0.2489

Anti-B cell	0 (0)	6 (42.9)	3 (33.3)	11 (84.6)	0.0092
No treatment	1 (25.0)	1 (7.1)	3 (33.3)	0 (0.0)	0.0950
Allograft survival time, days, median (IQR)	* (883 - *)	* (1221 - *)	1590 (160 - 2837)	2478 (1713 - 2478)	0.1661

Footnote: * out of observation time

Table 4 Pathological characteristics of PCAR among rejection types of Banff 2015 classification

Category	Borderline (N=4)	TCMR (N=14)	ABMR/sABMR (N=9)	TCMR/ABMR (N=13)	P-value
Interstitial inflammation: i score, median (IQR)	2 (1-2)	2 (2-2)	1 (1-2)	2 (2-3)	0.0009
Tubulitis: t score, median (IQR)	1 (1-1)	2 (2-3)	1 (0-2)	3 (2-3)	<0.0001
Vasculitis: v score, median (IQR)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-0)	0.2912
Glomerulitis; g score, median (IQR)	0 (0-0)	0 (0-0)	1 (1-2)	1 (1-2)	<0.0001
Peritubular capillaritis: ptc score, median (IQR)	1 (0-1)	1 (0-2)	2 (2-3)	2 (2-3)	0.0002
C4d on ptc: c4d score, median (IQR) [N=37]	0 (0-0)	0 (0-0)	1 (1-2)	1 (0-2)	0.0035
Chronic glomerulopathy: cg score, median (IQR)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-0)	0.0321
Arteriolar Hyalinosis: ah score, median (IQR)	1 (0-2)	0 (0-0)	2 (1-2)	1 (0-1)	0.0192
Hyaline arteriolar thickening: aah score, median (IQR)	0.5 (0-2)	0 (0-0)	1 (1-2)	0 (0-0)	0.0100
Vascular fibrous intimal thickening: cv score, median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.5566

Interstitial fibrosis: ci score, median (IQR)	1 (0-1)	0 (0-1)	2 (1-3)	0 (0-2)	0.0474
Tubular atrophy: ct score, median (IQR)	1 (0-1)	0 (0-1)	2 (1-3)	0 (0-2)	0.0212
Presense of TLO, N (%)	0 (0)	2 (14.3)	1 (11.1)	4 (30.7)	0.4254

Table 5 Risk factor of allograft loss in patients with PCAR according to Cox regression analysis

	HR	95% CI	P-value
Recipient age (per year)	0.98	0.94 – 1.02	0.3776
Cr at biopsy (per mg/dL)	1.87	1.07 – 3.35	0.0274
Biopsy time from transplantation >1 year	0.81	0.12 – 3.50	0.8000
DSA at biopsy	1.76	0.48 – 6.98	0.3858