Clin Transplant 2012: 26 (Suppl. 24): 25–31 DOI: 10.1111/j.1399-0012.2012.01641.x

Clinical Transplantation

Original Article

Pentraxin-3 expression in acute renal allograft rejection

Imai N, Nishi S, Yoshita K, Ito Y, Osawa Y, Takahashi K, Nakagawa Y, Saito K, Takahashi K, Narita I. Pentraxin-3 expression in acute renal allograft rejection.

Abstract: Pentraxin-3 (PTX3) is an acute phase reactant produced by a variety of cell types at sites of local inflammation. We examined by immunohistochemistry renal biopsies from patients with acute rejection (n = 10), protocol biopsies without rejection (n = 37), and peri-operative donor biopsies of the same transplant patients (n = 94) for intra-renal expression of PTX3, and its correlation with clinical, laboratory, and histopathologic parameters. PTX3 was mainly expressed in the interstitium of renal allograft. In the non-rejection biopsies (pre- and post-reperfusion and protocol biopsies), PTX3 expression area (PTX3%) was equally maintained at a low level, whereas in the rejection biopsies, PTX3% was significantly higher ($p < 0.0001$). Treatment of acute rejection resulted in a significant reduction of PTX3% ($p < 0.0001$). PTX3% positively correlated with the degree of allograft dysfunction and acute rejection scores of Banff classification (2009). This study suggests that PTX3% may be an available histological marker of acute renal allograft rejection.

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Key words: acute phase reactant – acute rejection – immunohistochemistry – inflammation – long pentraxin-3 (PTX3) – renal allograft – renal biopsy

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Conflict of interests: The authors do not have any relationships to disclose.

Accepted for publication 12 March 2012

Pentraxin-3 (PTX3), also known as TNF-inducible gene 14 protein (TSG-14), is a member of the pentraxin superfamily, which also includes C-reactive protein (CRP) and serum amyloid P-component. This superfamily characterized by a pentameric structure (1, 2). PTX3 is locally produced and released in response to inflammatory cytokines, such as IL-1 and TNF-alpha, by several cell types including vascular endothelial cells (3), smooth muscle cells (4), fibroblasts (5), adipocytes (6), dendritic cells (7), and macrophages (8). Neutrophils cannot produce PTX3, but they can store and release it into the bloodstream (9). Thus, PTX3 has been recently considered as a more specific biomarker indicating acute phase inflammation of local sites (10). Blood levels of PTX3 increase dramatically in critically ill patients, with a gradient from systematic inflammatory response syndrome to septic shock (11), and in several other diseases, such as mycocardial infarction (12), rheumatoid arthritis (13), atherosclerosis (4), small vessel vasculitis (14), and psoriasis (15). In addition, PTX3 protein expression in tissues has been confirmed on the vascular endothelial cells, smooth muscle cells, macrophages and neutrophils in acute myocardial infarction and aortic sclerosis (4). There have been only a few reports of PTX3 expression in renal tissue

(16–18). In this study, we examined the immunohistological expression of PTX3 in renal allograft biopsies and its availability as a marker of acute allograft rejection.

Patients and methods

Patients and graft biopsies

Forty-seven consecutive recipients who underwent kidney transplantation between January 2007 and December 2010 at Niigata University hospital were included. All recipients had a minimum of three renal allograft biopsies: pre-implantation, post-reperfusion, and protocol or episode biopsy. Pre-implantation biopsy was performed immediately after the removal of graft kidney during the perfusion with Collin's solution. Post-reperfusion biopsy was performed about one h after the reperfusion of allograft. Protocol biopsies were conducted in 37 recipients without clinical evidence of acute rejection (non-rejection group). These biopsies were performed just before discharge, at a mean post-operative days (POD) 35.9 ± 6.7 (range, 26–55). Ten recipients had acute allograft dysfunction and were diagnosed with acute rejection: T-cell mediated acute rejection in nine and antibody-mediated acute rejection in one (Banff 2009 criteria) (16) (rejection group). Episode biopsies were performed at an average POD 11.7 ± 10.4 (range, 4–37). Eight patients in the rejection group received a follow-up biopsy, after being treated for acute rejection, at an average POD 44.1 ± 9.6 (range, 33–55). The underlying kidney diseases of the recipients were: IgA nephropathy (18 cases), chronic glomerulonephritis (13 cases), focal segmental glomerulosclerosis (four cases), diabetic nephropathy (four cases), Alport's syndrome (two cases), hypertensive nephrosclerosis (two cases), reflux nephropathy (two cases), and congenital nephropathy (two cases). Informed consents for renal biopsy were obtained from all patients. Serum and urine samples were collected and measured at the day of biopsy by routine hospital methods. Clinical data were collected from medical records.

Histological method

The biopsy specimens were evaluated according to the standardized criteria of Banff working classification of kidney transplant pathology 2009 (19). Serial thin sections of formalin-fixed, paraffin-embedded tissues were prepared. For immunohistochemistry to detect PTX3, the sections were first deparaffinized, pretreated in a 10 mM citrate buffer (pH 6.0) under autoclave for 20 min. They were then incubated with 1:1000 rat anti-human PTX3 monoclonal antibody (Enzo Life Science Inernational, Inc., Plymouth Meeting, PA, USA) overnight at 4°C. After washing with 50 mM Tris-HCl buffer for 10 min, 1:100 horseradish peroxidase (HRP)-labeled anti-rat polyclonal rabbit antibody (DAKO, Kyoto, Japan) was added for one h at room temperature. Finally, diaminobenzidine and chromogen (DAKO) were used for visualizing HRP. Frozen specimens were stained using anti-human C4d antibody (Quidel Corporation, San Diego, California, USA) by the indirect immunofluorescence method. Detailed information on the immunohistological technique of C4d staining has been described in a previous report (20). We considered a case to be positive for C4d when the immunofluorescence signal was seen diffusely along the peritubular capillary (PTC) (Banff c4d score 3), whereas a focally positive finding was considered negative (Banff c4d score <3). The non-specific C4d deposition on PTC is often observed in the ABO blood type-incompatible allograft (21); therefore, the ABO-incompatible cases were excluded if using "c4d score" in the following study.

Morphometry for measuring PTX3%

For morphometric evaluation, serial sections were used to obtain photographs of PTX3 reaction and Masson-trichrome stain. Anti-PTX3 antibody-positive area was recognized by the brown color of diaminobenzidine, and the interstitial area in the cortex was decided by the blue color stained with Masson-trichrome. The percentage of PTX3 positive area (PTX3%) was calculated by dividing the anti-PTX3 antibody-positive area to the interstitial area using ImageJ Version 1.42q (National Institutes of Health, Research Services Branch, Bethesda, Maryland, USA) of morphometric application.

Statistical method

To investigate the relationship (SAS Institute Japan Ltd., Tokyo, Japan) between clinical or laboratory data and PTX3% values, we used regression analysis, unpaired t-test (Student's *t*-test), or Fisher's test. p values <0.05 were used as the criteria of statistically significant differences, and all analyses were conducted with JMP software version 8.0.2 (SAS Institute Japan Ltd., Tokyo, Japan).

Table 1. Recipients characteristics at the day of transplantation

	Non-rejection group (n = 37)	Rejection group (n = 10)	Significance
Recipient age (yr)	39.1 ± 14.7	41.9 ± 8.6	n.s.
Donor: parent/ sibling/spouse	24/2/11	4/1/5	n.s.
Donor age (yr)	56.2 ± 10.3	51.6 ± 7.4	n.s.
ABO blood type: compatible/ incompatible	23/14	3/7	n.s.
HLA mismatch number 1/2/3/4/5/6	5/11/14/4/2/1	0/0/6/2/2/0	n.s.
White blood cell (number × $10^3/\mu L$)	6.1 ± 2.0	6.3 ± 2.8	n.s.
Urea nitrogen (mg/dL)	48.4 ± 18.2	47.1 ± 21.0	n.s.
Serum creatinine (mg/dL)	9.1 ± 2.9	10.2 ± 1.9	n.s.
Uric acid (mg/dL)	8.8 ± 16.0	10.0 ± 11.5	n.s.
CRP (mg/dL)	0.36 ± 1.32	0.01 ± 0.01	n.s.
eGFR (mL/min/1.73 m^2)	5.6 ± 2.1	4.9 ± 1.7	n.s.
ah score (Banff '09): score 1/2/3/4	34/3/0/0	7/2/1/0	n.s.

eGFR, estimated glomerular filtration rate; n.s., not significant.

Results

Table 1 compares the recipients' characteristics and baseline laboratory data at transplantation in the non-rejection and rejection group. There were no differences in recipient age, familiar relationship with the donor, donor age, frequency of ABO blood type incompatibility, HLA mismatch number, peripheral white blood cell (WBC) count, serum levels of creatinine, uric acid, CRP, and estimated glomerular filtration rate (eGFR) between the two groups. Banff scores between the two groups were also not different (data not shown). Clinical and laboratory data at post-transplant biopsy in the groups with and without rejection were shown in Table 2. The rejection group had higher levels of blood urea nitrogen, serum creatinine, CRP, proteinuria and a higher frequency of hematuria, but lower urine volume and eGFR than non-rejection group. There was significant reduction in the levels of blood urea nitrogen, serum creatinine, eGFR, frequency of hematuria at the follow-up biopsy.

PTX3 expression and PTX3%

Anti-PTX3 antibody mainly reacted to the cortical interstitium between tubuli of renal allograft. Infiltrated cells into glomeruli were also positive for anti-PTX3 antibody (Fig. 1). PTX3 expression in the peri-operative and protocol biopsies was nil or weak. The average PTX3% in the non-rejection group was not different between the pre-implantation (mean ± SD: 0.6 ± 0.7%), post-reperfusion (0.5 ± 0.5%), or protocol biopsies (1.3 ± 1.2%). In rejection group, the average of PTX3% in the biopsies with acute rejection (25.9 ± 15.1%) was significantly higher than protocol ($p < 0.0001$) pre-implantation (0.8 ± 0.6%) ($p < 0.0001$) and post-reperfusion biopsies (1.0 ± 1.6%) ($p < 0.0001$). PTX3% decreased significantly in the follow-up biopsies following treatment of acute rejection (4.5 ± 3.2%) ($p < 0.0001$) (Fig. 2).

Correlation of PTX3% with clinicopathologic data

The average PTX3% of all post-transplant biopsies correlated positively with the levels of blood urea nitrogen, serum creatinine, CRP, and urine protein excretion and negatively with the eGFR and urine volume. There were no association between PTX3% and peripheral WBC count, serum uric acid and urine creatinine level (Table. 3). The average PTX3% correlated with the scores of "i", "v", "ptc" and "c4d", while "t", "g" and each of chronic Banff scores (ci, ct, cg, mm, cv, ah, ti, aah, ptcbm) showed no association with PTX3% (Table. 4). The correlation of the average PTX3% between "c4d score 0" and "c4d score 1" was found, but these both scores were considered negative in our definition. Therefore, the average PTX3% was determined to be independent of the C4d deposition on PTC.

Discussion

The long PTX3 is considered to be important in the regulation of inflammation and innate immunity. The present study clearly indicated that PTX3 expression is up-regulated in acute rejection and was correlated with the severity of rejection both clinically and pathologically.

The origin of PTX3 in the kidney is not entirely clear. Cultured glomerular epithelial cells can produce PTX3 *in vitro* (17). However, cultured human mesangial cells have also been shown to synthesize PTX3 when stimulated with TNF-α and IgA (16). Several studies have demonstrated the immunohistochemical localization of PTX3 protein in human kidney in mesangial area, inflammatory cells infiltrating glomeruli, interstitium and peritubular capillaries in both primary and secondary glomerulonephritis (16, 17). In our study, PTX3 was predominantly observed in the interstitium and infiltrating glomerular cells, which is in keeping with a previous report (18).

Table 2. Recipients data at the day of post-transplant biopsy

	Non-rejection group at the protocol biopsy (n = 37)	Rejection group	
		At the episode biopsy (n = 10)	At the follw-up biopsy (n = 8)
Post-operative days (d)	39.1 ± 14.7	41.9 ± 8.6	44.1 ± 9.6*
White blood cell (number × $10^3/\mu L$)	6.2 ± 2.3	6.5 ± 2.2	6.6 ± 3.4
Urea nitrogen (mg/dL)	16.6 ± 5.4*	47.7 ± 26.7	22.1 ± 7.1*
Serum creatinine (mg/dL)	1.3 ± 0.5*	4.0 ± 2.4	1.3 ± 0.5*
Uric acid (mg/dL)	6.7 ± 1.4	7.6 ± 2.2	6.9 ± 1.4
eGFR (mL/min/1.73m^2)	48.6 ± 14.7*	19.1 ± 12.7	43.4 ± 12.8*
CRP (mg/dL)	0.07 ± 0.19*	1.60 ± 2.39	0.05 ± 0.10
Urine volume (mL/d)	1841 ± 418*	1114 ± 746	1864 ± 673
Proteinuria (g/d)	0.14 ± 0.16*	0.79 ± 0.24	0.38 ± 0.40
Hematuria: positive/negative	5/32*	7/2	1/7*
Urine creatinine (mg/dL)	98.6 ± 181.0	87.4 ± 42.2	59.5 ± 28.4

eGFR, estimated glomerular filtration rate.
*Significant difference ($p < 0.05$) compared to data at the episode biopsy.

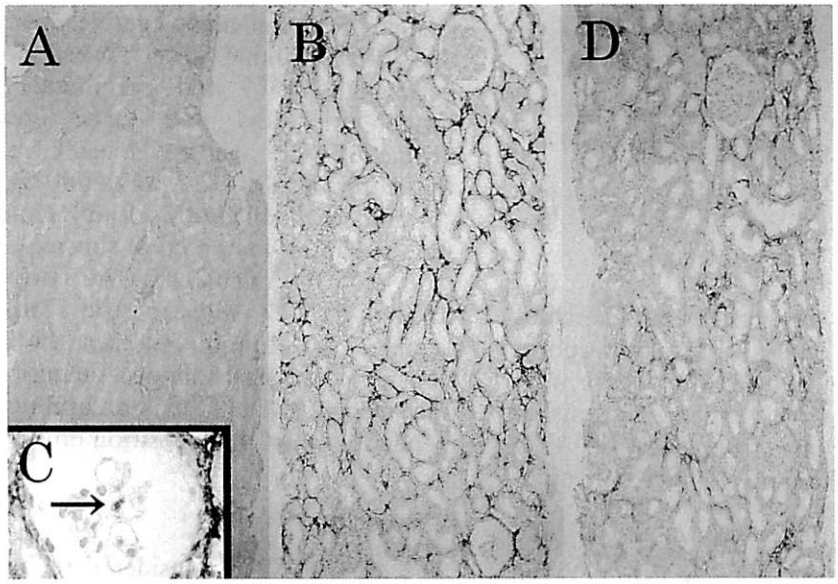

Fig. 1. Typical microphotographs of anti-PTX3 antibody immunostaining from same recipient: (Panel A, original magnification × 40) post-reperfusion biopsy with negative staining; (Panel B, original magnification × 40) Acute rejection biopsy showing positive staining in the interstitium; (Panel C, arrow, original magnification × 400) Positively stained infiltrated multinucleated cell in glomerulus from same specimen in panel B; (Panel D, original magnification × 40) Follow-up biopsy showing less positive reaction compared to rejection biopsy.

The function of PTX3 as an acute and early phase protein in inflammation is well-established. It can activate complement system by binding to trigger proteins, such as C1q (22), mannose-binding lectin (MBL) (23), L-ficolin (24), M-ficolin (25), and is believed to contribute to innate immunity. Moreover, PTX3 helps in the removal of apoptotic cells (26), and to tissue repair and remodeling (27). The role of PTX3 in acute allograft rejection remains unclear. The enhanced expression of PTX3 in the interstitium of rejection biopsies suggests that it may contribute to the inflammation in acute rejection. However, what causes the up-regulation of PTX3 in acute rejection also remains an open question. In this study, we could not identify which cells were involved in the production of PTX3. It has been reported that any of following cells can produce PTX3: vascular endothelial cells (3), smooth muscle cells (4), fibroblasts (5), adipocytes (6), dendritic cells (7), macrophages (8), and tubular epithelial cells (18). An alternative explanation for the positive staining for PTX3 in the interstitium is that PTX3 may be released from a PTX3-producing cell and depos-

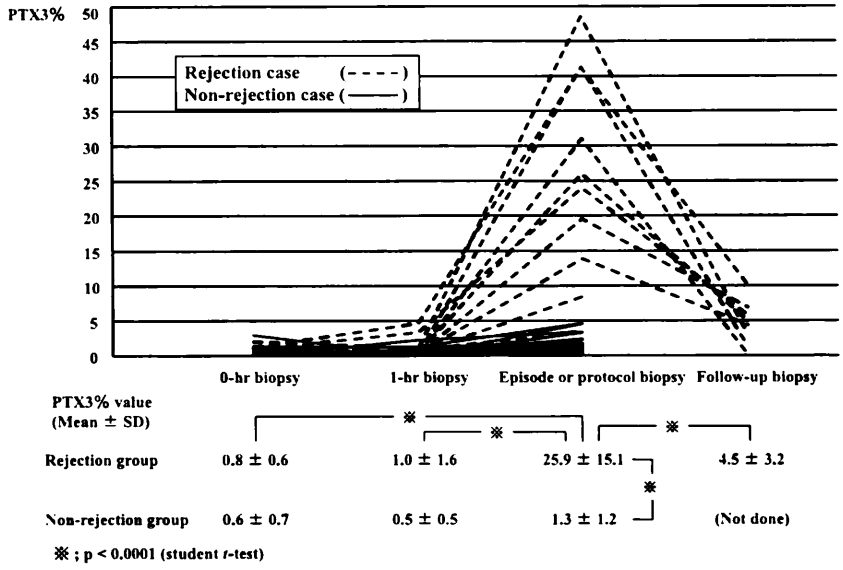

Fig. 2. Changes of PTX3% in all individual recipients with (dashed line) and without (solid line) rejection at each biopsy.

Table 3. Relationship of PTX3% and clinical data at the day of post-transplant biopsy (regression analysis)

	R^2-value	p-value	Linear equation	Significance
Post-operative days (d)	0.471362	<0.0001	=−0.78 × PT×X3% + 37.5	Significant
White blood cell (number × $10^3/\mu L$)	0.000139	0.932	=2.48 × PTX3% + 6284	n.s.
Urea nitrogen (mg/dL)	0.482863	<0.0001	=1.03 × PTX3% + 16.64	Significant
Serum creatinine (mg/dL)	0.479494	<0.0001	=0.09 × PTC3% + 1.234	Significant
Uric acid (mg/dL)	0.017571	0.3347	=0.02 × PTX3% + 6.81	n.s.
eGFR ($mL/min/1.73m^2$)	0.380732	<0.0001	=−0.97 × PTX3% + 48.47	Significant
CRP (mg/dL)	0.121418	0.0114	=0.04 × PTX3% + 0.132	Significant
Urine volume (mL/d)	0.334236	0.0002	=−34.8 × PTX3% + 1901	Significant
Proteinuria (g/)	0.419386	<0.0001	=0.02 × PTX3% + 0.14	Significant
Urine creatinine (mg/dL)	5.026^{-5}	0.9594	=−0.10 × PTX3% + 91.5	n.s.

eGFR, estimated glomerular filtration rate; n.s., not significant.

Table 4. PTX3% value of the each banff scores (Student t-test)

Banff score	0 mean ± SD (n)	1 mean ± SD (n)	2 mean ± SD (n)	3 mean ± SD (n)	Significance
t	3.5 ± 7.8 (30)	7.6 ± 12.2 (18)	16.9 ± 27.8 (3)	12.1 ± 11.6 (4)	n.s.
i	3.0 ± 6.8 (41)	11.0 ± 13.8 (10)	13.8 ± 14.7 (2)	40.1 ± 12.6 (2)	0 vs. 1.2.3, 1.2 vs. 3
g	5.9 ± 11.0 (53)	15.6 ± 12.0 (2)	(0)	(0)	n.s.
v	4.9 ± 10.1 (51)	23.1 ± 15.2 (4)	(0)	(0)	0 vs. 1
ptc	3.0 ± 6.8 (40)	3.5 ± 2.2 (5)	23.7 ± 18.9 (7)	13.3 ± 11.7 (3)	0 vs. 2.3, 1 vs. 2
c4d*	0.6 ± 0.4 (14)	6.3 ± 9.9 (13)	(0)	0.3 (1)	0 vs. 1
ci	6.3 ± 11.7 (51)	4.8 ± 6.3 (4)	(0)	(0)	n.s.
ct	6.3 ± 11.6 (51)	0.3 (4)	4.9 (1)	(0)	n.s.
cg	6.2 ± 11.5 (54)	4.9 (1)	(0)	(0)	n.s.
mm	6.2 ± 11.4 (55)	(0)	(0)	(0)	
cv	6.3 ± 11.6 (53)	0.3 (1)	4.9 (1)	(0)	n.s.
ah	6.4 ± 12.2 (45)	2.0 ± 1.4 (7)	12.6 ± 7.8 (3)	(0)	n.s.
ti	6.1 ± 11.4 (51)	8.1 ± 12.3 (4)	(0)	(0)	n.s.
aah	6.2 ± 11.4 (54)	(0)	(0)	(0)	
ptcbm	6.0 ± 11.4 (53)	19.6 (1)	4.9 (1)	(0)	n.s.

n.s., not significant.
*Exclude ABO-blood type incompatible cases.

ited in the interstitial collagen fibers of renal allograft. Similar interstitial deposition of PTX3 was observed in heart tissue with myocardial infarction (28).

In a mouse model of acute myocardial infarction. PTX3 played a cardioprotective role to ischemia-reperfusion stress PTX3 mRNA expression in the heart started four h after ischemia. peaked at 16 h. and declined thereafter (29). It is conceivable that PTX3 might have a similar renoprotective effect to ischemia-reperfusion injury to that seen in the heart. However. PTX3 expression was weak in both pre-implantation and post-perfusion 1-hr biopsies. It is possible that a longer time is needed before PTX3 up-regulation following ischemia reperfusion.

In this study. we have demonstrated the up-regulated expression of PTX3 in acute allograft rejection. which positively correlated with the severity of graft dysfunction and histological Banff scores. suggesting that PTX3 may have a role in acute rejection. Future studies. including biochemical and genetic analysis of PTX3, and *in situ* hybridization are necessary to delineate the exact role of PTX3 in acute rejection.

Acknowledgement

The authors are grateful to Dr. Bassam Alchi. MRCP, PhD. (Renal unit. Addenbrooke's hospital, Cambridge, UK) for his linguistic assistance. This study was supported in part by a Grant-in-Aid for Progressive Renal Diseases Research. Ministry of Health, Labour and Welfare of Japan.

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