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Brief Communication

Elevated Plasma Long Pentraxin-3 Levels and Primary Graft Dysfunction After Lung Transplantation for Idiopathic Pulmonary Fibrosis

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Primary graft dysfunction (PGD) after lung transplantation may result from ischemia reperfusion injury (IRI). The innate immune response to IRI may be mediated by Toll-like receptor and IL-1-induced long pentraxin-3 (PTX3) release. We hypothesized that elevated PTX3 levels were associated with PGD. We performed a nested case control study of lung transplant recipients with idiopathic pulmonary fibrosis (IPF) or chronic obstructive pulmonary disease (COPD) from the Lung Transplant Outcomes Group cohort. PTX3 levels were measured pretransplant, and 6 and 24 h postreperfusion. Cases were subjects with grade 3 PGD within 72 h of transplantation and controls were those without grade 3 PGD. Generalized estimating equations and multivariable logistic regression were used for analysis. We selected 40 PGD cases and 79 non-PGD controls. Plasma PTX3 level was associated with PGD in IPF but not COPD recipients (p for interaction < 0.03). Among patients with IPF, PTX3 levels at 6 and 24 h were associated with PGD (OR = 1.6, p = 0.02 at 6 h; OR = 1.4, p = 0.008 at 24 h). Elevated PTX3 levels were associated with the development of PGD after lung transplantation in IPF patients. Future studies evaluating the role of innate immune activation in IPF and PGD are warranted.

Key words: Idiopathic pulmonary fibrosis, long pentraxin-3, lung transplantation, primary graft dysfunction

Abbreviations: ALI, acute lung injury; BOS, bronchiolitis obliterans syndrome; CC16, clara cell secretory protein; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; GEE, generalized estimating equations; IRI, ischemia reperfusion injury; ISHLT, international society for heart and lung transplantation; LPS, lipopolysaccharide; LTOG, lung transplant outcomes group; OR, odds ratio; PASP, pulmonary arterial systolic pressure; PGD, primary graft dysfunction; IPF, idiopathic pulmonary fibrosis; PRBC, packed red blood cell; PTX3, long pentraxin-3; SAP, serum amyloid P component; TF, tissue factor; TNF-α , tissue necrosis factor-alpha.

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Introduction

Ischemia reperfusion injury (IRI) plays a role in initiating primary graft dysfunction (PGD), activating and altering cellular pathways involved in immune activation and leading to an acute respiratory distress-like clinical phenomenon (1–3). The role of innate immune activation after IRI in lung transplant recipients is poorly understood.

Innate immune activation plays a role in the propagation of IRI in transplanted solid organs (4–7). IRI involves Toll-like receptor (TLR) signaling pathways, complement activation and natural killer cell migration in cardiac transplantation models and may lead to decreased allograft tolerance and the later development of accelerated cardiac allograft vasculopathy (4,5). Innate immune activation as a result of IRI has also been identified to contribute to renal and hepatic allograft dysfunction (6,7).

Long pentraxin-3 (PTX3) is a member of a phylogenetically conserved group of acute phase reactants that are involved in inflammation and innate immunity. A previous study of plasma cytokines and PGD demonstrated that plasma levels of other acute phase reactants, including tumor necrosis factor alpha and interferon gamma, decreased after transplant and were not associated with risk of PGD (8). PTX3 is produced at the site of inflammation by cells implicated in the pathogenesis of PGD and has been shown to be elevated in other pathologic conditions related to both ischemia and inflammation, notably acute myocardial infarction and acute lung injury (ALI) (9–11).

Abnormal activation of innate immunity in response to IRI may be mediated by Toll-like receptors and IL-1-induced PTX3 release. Consequently, higher PTX3 levels may play a role in PGD pathogenesis or be a marker of innate immune activation. We therefore hypothesized that elevated PTX3 levels would be associated with PGD. In addition, we sought to identify differences in the association of PGD with PTX3 levels across the two most common indications for lung transplantation, idiopathic pulmonary fibrosis (IPF) and chronic obstructive pulmonary disease (COPD).

Materials and Methods

Subject selection

All study subjects were randomly selected from within the ongoing Lung Transplant Outcomes Group (LTOG) cohort, a 13-center, prospective study that has been described previously (12,13). A multicenter, nested case control study design was selected over a cohort study because of the significant expense and sample volume required for evaluating PTX3 plasma concentrations. Cases and controls were randomly selected from the greater than 1100 patients enrolled in the LTOG cohort. Blood samples were collected from all cohort participants before transplant and at 6 and 24 h after transplantation. Patient-level clinical data were collected prospectively and plasma samples were centrifuged within 30 min and then stored at −80°C for biomarker measurement. The institutional review boards at each site approved this study. Informed consent was obtained from each subject at the time of enrollment in the cohort.

Subjects with grade 3 PGD that developed within 72 h of allograft reperfusion were considered as cases. Subjects with grade 0–2 PGD but without grade 3 PGD at any time after lung transplantation were considered as controls. This case definition of PGD has been previously validated and used extensively in the literature (14,15). Sensitivity analysis was performed using highest PGD grade within the first 72 h after allograft reperfusion as an ordinal variable.

Patients with a reported predisposing diagnosis of IPF or COPD were eligible for inclusion. To eliminate the possibility of small subgroups, ensure the groups were comparable, and to allow for within diagnosis analyses, the cases and controls were frequency matched for these predisposing diagnoses. We chose the two most common indications for transplantation to minimize combinations of diagnoses and aid in matching.

PGD grade determination

PGD grades were assigned based on International Society for Heart and Lung Transplant (ISHLT) guidelines as previously described (13). Chest X-rays from immediately after transplant and from 24, 48 and 72 h after transplant were examined independently by two trained physicians with grades assigned for each radiograph (classification $\kappa = 0.95$). As defined by the ISHLT guidelines, grade 3 PGD is the presence of diffuse alveolar infiltrates with a PaO_2/FiO_2 ratio <200 and the exclusion of secondary causes (14,16).

Measurement of PTX3 concentration

Plasma PTX3 concentrations were determined in duplicate using a sandwich enzyme-linked immunosorbent assay (Alexis Biochemicals, Lausen, Switzerland). The intraassay coefficient of variation for this assay was 5.7%. All laboratory personnel were unaware of the PGD status of study subjects.

Statistical analysis

Study subject characteristics were compared using two sample *t*-tests or Wilcoxon rank sum tests as appropriate. Proportions were compared using two-group proportion tests whereas characteristics with greater than two variables were assessed with Kruskal–Wallis rank tests as described previously (15). Primary analysis was performed using generalized estimating equations (GEE) to identify differences in PTX3 levels over time and across study subjects. Secondary analyses included using Wilcoxon rank sum tests across groups and multivariable logistic regression modeling. Based on previous studies identifying differences in biomarker levels across predisposing diagnoses, we *a priori* defined diagnosis leading to transplantation as a possible effect modifier and performed diagnosis specific analyses (15). Recipient and donor age, sex, race/ethnicity, cardiopulmonary bypass use, transplant surgical type, ischemic time, intraoperative pulmonary artery systolic pressure (PASP), packed red blood cell (PRBC), platelet and plasma transfusion volumes were included as possible confounders in multivariable logistic models. A change in odds ratio (OR), after inclusion of a covariate, of greater than 20% was used to identify confounding. Sensitivity analysis evaluating the association of PTX3 concentration with the highest PGD grade on any day was preformed using ordinal logistic regression. A $p < 0.05$ was predefined for statistical significance for all tests. We defined the presence of effect modification *a priori* by a $p < 0.1$. All statistical analyses were performed using Stata 11.1 software (STATA Corp., College Station, TX, USA).

Table 1: Subject characteristics stratified for PGD cases and non-PGD controls

Characteristics	PGD (n = 40)	Non-PGD (n = 79)	p-Value
Recipient			
Age (year)	55 (52, 58)	56 (53, 58)	0.7
Female	30%	46%	0.1
Race			0.1
Caucasian	80%	90%	
African American	13%	5%	
Hispanic	0%	4%	
Asian	5%	1%	
Other	3%	0%	
Donor			
Age (year)	34 (29, 38)	33 (30, 36)	0.7
Female	48%	43%	0.6
Race			0.2
Caucasian	73%	62%	
African American	15%	22%	
Hispanic	13%	9%	
Asian	0%	6%	
Other	0%	1%	
Cause of death			0.9
Blunt trauma	3%	4%	
Head trauma	30%	35%	
Suicide	3%	0%	
Stroke	48%	34%	
Anoxia	0%	11%	
Other	18%	15%	
Recipient diagnosis			0.9
COPD	40%	41%	
IPF	60%	59%	
Transplant type, single	38%	38%	0.9
Use of cardiopulmonary bypass	54%	30%	0.01
Time on bypass (min)	235 (201, 270)	210 (184, 236)	0.2
Ischemic time (min)	308 (281, 334)	282 (262, 302)	0.1
Pulmonary artery systolic pressure (mmHg)	47 (40, 54)	41 (36, 46)	0.2
Packed red blood cells (mL)	1063 (675, 1450)	696 (538, 854)	0.04
Fresh frozen plasma (mL)	893 (702, 1084)	1062 (769, 1354)	0.3
Platelets (mL)	421 (99, 743)	228 (46, 411)	0.3

PGD is defined as any grade 3 PGD during first 72 h. Continuous variables are expressed as means with 95% confidence intervals, whereas dichotomous and categorical variables are expressed as percentages, which may not exactly total 100% because of rounding.

Results

We included 40 PGD cases and 79 non-PGD controls (Table 1). One control sample was excluded from analysis because of spurious results on the standard curve. A higher percentage of PGD cases required cardiopulmonary bypass than controls (54% vs. 30%; $p = 0.01$) and PGD cases received a larger volume of intraoperative PRBCs than controls (1063 mL vs. 696 mL; $p = 0.04$), but cases and controls were otherwise similar. There were 16 PGD cases and 32 non-PGD controls with COPD, and 24 PGD cases and 47 non-PGD controls with IPF. Although pretransplant PTX3 levels were low compared to posttransplant levels in all patients, pretransplant levels were significantly higher in subjects with IPF (2.1 ng/mL; IQR 1.3, 7.0) compared to subjects with COPD (0.8 ng/mL; IQR 0.5, 2.0; $p < 0.001$).

Among all enrolled subjects, GEE modeling identified a nonsignificant difference in the trend of PTX3 levels across all the three time points between cases and controls ($\beta = 0.09$, 95% CI −0.005, 0.2; $p = 0.06$; Figure 1A). The association between median PTX3 concentration and PGD differed according to predisposing diagnosis (p for interaction <0.03). There was no significant difference in PTX3 concentration between COPD cases and controls at any time point (all $p > 0.08$). GEE longitudinal modeling identified a significant difference in the trend of PTX3 levels across all the three time points between IPF cases and controls ($\beta = 0.3$; 95% CI 0.1, 0.5; $p = 0.001$) but not COPD cases and controls ($\beta = -0.2$; 95% CI −0.5, 0.1; $p = 0.2$; Figures 1B and C). PTX3 levels were significantly higher in IPF patients with PGD compared to non-PGD IPF controls at 6 h (45.7 ng/mL vs. 18.0 ng/mL; $p = 0.02$) and 24 h (88.9 ng/mL vs. 22.7 ng/mL; $p = 0.007$) after reperfusion.

When subjects were analyzed according to diagnosis, there was a significant association between PTX3 level and the odds of PGD at 6 h (OR for each 50 ng/mL higher

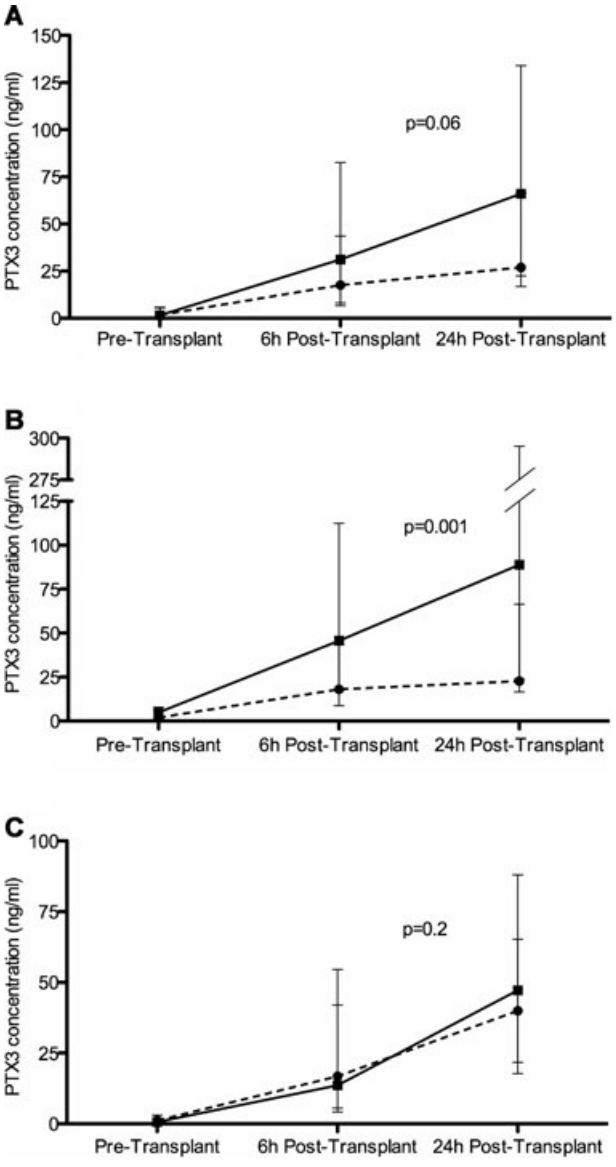

Figure 1: Longitudinal median PTX3 level across the pretransplant, 6-h posttransplant, and 24-h posttransplant time points. (A) All study subjects, (B) subjects with IPF and (C) subjects with COPD. Solid line represents PGD cases and dashed line represents PGD-free controls. Error bars represent the 95% CI. p-Value reported is from GEE modeling.

level = 1.6; 95% CI 1.1, 2.5; p = 0.02) and 24 h (OR for each 50 ng/mL higher level = 1.3; 95% CI 1.1, 1.7; p = 0.008) for IPF patients but no association for subjects with COPD at any time point ($p > 0.30$). Evaluation for possible confounding was performed on the IPF subgroup at 6 and 24 h postreperfusion (Table 2). At 6 h, use of cardiopulmonary bypass attenuated the association of PTX3 level with PGD. There was no attenuation of this relationship by any covariates for PTX3 levels measured at 24 h after reperfusion. Surgical transplant type was similarly distributed among both COPD and IPF recipients in this study and transplant type was not found to be a confounder of the relationship between PTX3 and PGD.

A sensitivity analysis using highest PGD grade on any day as an ordinal outcome was performed. There was a significant increase in PTX3 level at 24 h with increasing severity of PGD ($p = 0.048$; Figure 2). This relationship was significant in the IPF subgroup ($p = 0.006$) but not the COPD subgroup ($p = 0.8$).

Pulmonary hypertension and use of cardiopulmonary bypass have been previously identified as risk factors for PGD (17). Although idiopathic pulmonary arterial hypertension patients were not included in this study, PASP among study subjects ranged from 13 to 111 mmHg. Spearman rank correlation revealed PASP was not significantly associated with PTX3 level before transplant ($\rho = 0.15$; $p = 0.1$), or at 6 h ($\rho = 0.14$; $p = 0.2$) or 24 h ($\rho = 0.19$; $p = 0.06$) after reperfusion.

Discussion

We found that elevated PTX3 levels were associated with an increased risk of PGD in lung transplant recipients with IPF but not COPD. Longitudinal analysis in the IPF subgroup identified a significant difference in trend over time of PTX3 levels in patients with PGD compared to non-PGD controls. Furthermore, the relationships between PGD and PTX3 levels in the IPF group were independent of most donor, recipient and surgical characteristics, including PASP, ischemic time and surgical transplant type, in multivariable modeling. This study provides clinical evidence of a role for activation of innate immune pathways in the pathogenesis of PGD after lung transplantation.

We identified a significant association between PTX3 level and PGD in the IPF subgroup, with pretransplant PTX3 levels being significantly higher in patients with IPF compared to those with COPD. A registry study demonstrated recipient pretransplant diagnosis of IPF to be independently associated with increased risk for PGD when compared to subjects with COPD (17). To our knowledge, there are no previous studies investigating the role of PTX3 in IPF patients. We have previously shown that pretransplant CC16 levels were higher in IPF recipients than in COPD recipients and that posttransplant trends in CC16 levels differed in patients with IPF compared with other indications for transplant (15). The IPF-specific association of elevated PTX3 level and PGD may provide further evidence that posttransplant biomarker profiles and important cellular pathways for the development of PGD are likely dependent on pretransplant diagnoses.

In the IPF subgroup, we identified a significant difference between the longitudinal trend in PTX3 levels between cases and controls, with significant univariate differences

Table 2: Odds ratios for the development of Primary Graft Dysfunction in logistic regression models

Model	Odds ratio per 50 ng/mL increase in PTX3, 6 h (95% CI)	p-Value	Odds ratio per 50 ng/mL increase in PTX3, 24 h (95% CI)	p-Value
Unadjusted base model (n = 119)	1.1 (0.9, 1.3)	0.5	1.1 (1.0, 1.3)	0.07
COPD only (n = 48)	0.8 (0.5, 1.3)	0.3	0.9 (0.7, 1.2)	0.5
IPF only (n = 71)	1.6 (1.1, 2.5)	0.02	1.4 (1.1, 1.7)	0.008
IPF adjusted for				
Cardiopulmonary bypass (n = 71)	1.5 (1.0, 2.2)	0.09	1.3 (1.0, 1.6)	0.02
Transplant type (n = 71)	1.7 (1.1, 2.6)	0.02	1.4 (1.1, 1.8)	0.008
Recipient age (n = 71)	1.7 (1.1, 2.6)	0.02	1.4 (1.1, 1.7)	0.008
Recipient sex (n = 71)	1.6 (1.1, 2.5)	0.03	1.4 (1.1, 1.7)	0.008
Recipient race/ethnicity (n = 71)	1.6 (1.0, 2.4)	0.05	1.4 (1.1, 1.9)	0.01
Donor age (n = 70)	1.6 (1.0, 2.4)	0.03	1.4 (1.7, 1.7)	0.009
Donor mode of death (n = 66)	1.6 (1.0, 2.4)	0.04	1.3 (1.1, 1.7)	0.01
Donor sex (n = 71)	1.6 (1.1, 2.5)	0.03	1.4 (1.1, 1.8)	0.007
Donor race/ethnicity (n = 71)	1.7 (1.0, 2.7)	0.03	1.6 (1.1, 2.2)	0.01
Total ischemic time (n = 67)	1.9 (1.1, 3.5)	0.03	1.4 (1.1, 1.7)	0.02
PASP (n = 62)	1.5 (1.0, 2.3)	0.05	1.7 (1.1, 2.5)	0.01
Packed red blood cells (n = 66)	1.7 (1.1, 2.7)	0.03	1.4 (1.1, 1.7)	0.01
Platelets (n = 55)	1.9 (1.1, 3.5)	0.03	1.5 (1.1, 2.1)	0.009

Odds ratios for the development of primary graft dysfunction in logistic regression models per 50 ng/mL increase in PTX3. COPD = chronic obstructive pulmonary disease; IPF = idiopathic pulmonary fibrosis; PASP = pulmonary arterial systolic pressure.

at 6 h and 24 h after transplant. This time course fits with a previous study demonstrating PTX3 levels peaking at 7.5 h after CCU admission for myocardial infarction (9). In addition, continued inflammatory insults can result in prolongation of elevated PTX3 levels as seen in a cohort study of critically ill medical intensive care unit patients (18). In our study, whereas the most significant increase in PTX3 occurred in patients with PGD, PTX3 levels increased in all study subjects, regardless of outcome, implying an association with IRI, even at lower levels of severity, in patients without PGD. We do not have measurements of PTX3 levels at later time points to further assess trends over time.

There are several limitations to our study. First, there is the potential for limited generalizability. Although our findings were most significant in the subpopulation of subjects with IPF compared to those with COPD, other diagnoses were not included in the study. Given the documented production and release of PTX3 from vascular endothelial cells and the significant association of recipient pulmonary hypertension with PGD, elevated PTX3 plasma levels may

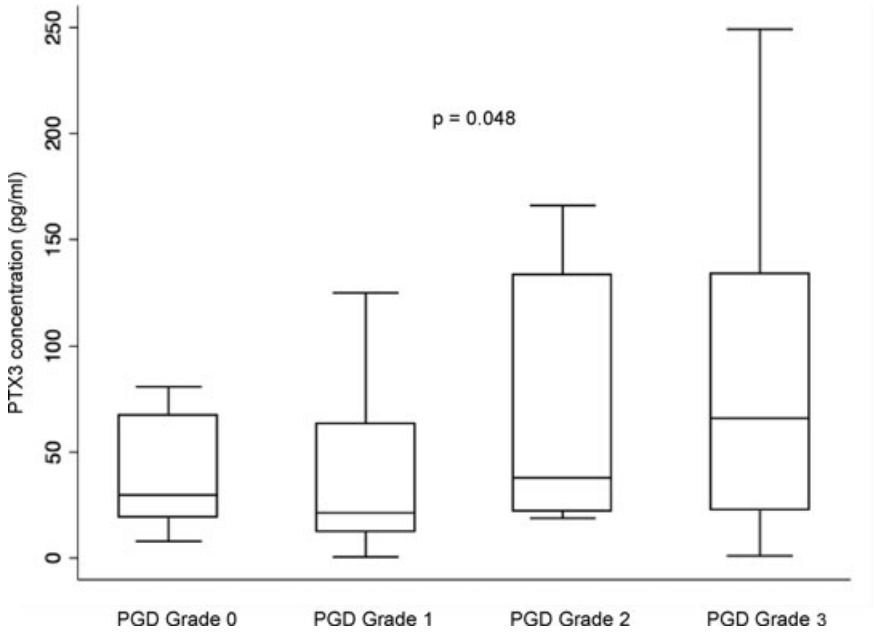

Figure 2: Median plasma PTX3 concentration 24 h after transplant in all patients stratified by the highest PGD grade developing in the first 72 h. Horizontal line indicates median concentration. The upper and lower limits of the box indicate the interquartile range. p-Value reported is determined from ordinal logistic regression modeling.

be important in PGD pathogenesis in other predisposing diagnoses. In addition, whereas the association of PTX3 level and PGD was not significant in the COPD subgroup, the small sample size in the COPD-only group may have led to a false-negative result. In this study, we were unable to identify a correlation between PASP and PTX3 level at any time point. There is also the potential for PGD misclassification. Although the case control format limits the ability to perform more extensive sensitivity analyses, an analysis with an outcome of highest PGD grade in the 72 h after reperfusion demonstrated a significant association between worsening grade from 0 to 3 and increased PTX3 plasma level. As with previous biomarker studies, given similar preoperative PTX3 levels between cases and controls, it is not possible to define a causal relationship of PTX3 production and release leading to PGD. However, the concordance of PTX3 level with PGD supports a mechanistic role for innate immune activation in the development of PGD. Although we controlled for identified confounders, we were unable to control for airway infection or pre- and posttransplant bacterial colonization. Given the integral role for PTX3 in innate immune responses and response to infection, it is possible that PTX3 is a marker for infection and that bacterial infection is the link with severe PGD. PTX3 production by antigen presenting cells is inducible by *Pseudomonas aeruginosa* and *Aspergillus fumigatus* and PTX3 has been shown to directly bind CMV (19). However, the 3-day postoperative time frame for developing PGD makes clinically significant airway infection an unlikely explanation for our findings, unless subclinical infection preexisted in the donor. A previous study demonstrated that positive donor gram stain is not associated with the development of early postoperative pneumonia or worsening oxygenation after transplant (20). Furthermore, infection with *Pseudomonas*, *Aspergillus* and CMV occur later in the posttransplant period and are associated with increased rates of BOS, not PGD.

In summary, we identified elevated PTX3 plasma concentrations to be strongly associated with postlung transplant PGD in patients with IPF. This provides support for a mechanistic role for innate immune activation in the development of severe PGD. Elucidating differences in innate immune activation in IPF compared to COPD in lung transplant recipients is an area of future study.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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