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Elevated Levels of Systemic Pentraxin 3 Are Associated With Thin-Cap Fibroatheroma in Coronary Culprit Lesions

Assessment by Optical Coherence Tomography and Intravascular Ultrasound

Seiji Koga, MD,* Satoshi Ikeda, MD,* Takeo Yoshida, MD,* Tomoo Nakata, MD,* Masayoshi Takeno, MD,* Nobuhito Masuda, PHD,† Yuji Koide, MD,* Hiroaki Kawano, MD,* Koji Maemura, MD*

Nagasaki and Tokyo, Japan

Objectives This study sought to determine whether systemic levels of pentraxin 3 (PTX3), a novel inflammatory marker, are associated with thin-cap fibroatheroma (TCFA).

Background Biomarkers predicting the presence of TCFA in vivo have not been established.

Methods We evaluated 75 patients (stable angina pectoris, n = 47; acute coronary syndrome, n = 28) with de novo culprit lesions who were examined by optical coherence tomography and intravascular ultrasound. We defined TCFA as lipid-rich plaque with a fibrous cap <65 μm thick. Systemic levels of PTX3 were compared between patients with and without TCFA.

Results Thirty-eight and 37 patients with and without TCFA, respectively, were identified. Levels of PTX3 were significantly higher in patients with than in those without TCFA ($p < 0.001$) and correlated inversely with fibrous cap thickness ($r = -0.71$, $p = 0.001$) and positively with the remodeling index ($r = 0.25$, $p = 0.037$). Multivariate logistic regression analysis showed that a higher PTX3 level was the most powerful predictor of TCFA (odds ratio: 3.26, 95% confidence interval: 1.75 to 6.05, $p < 0.001$). Receiver-operating characteristic curve analysis showed that >3.24 ng/ml of PTX3 could predict TCFA with 84% sensitivity and 86% specificity.

Conclusions Higher levels of systemic PTX3 are associated with TCFA. Systemic PTX3 levels comprise a useful inflammatory marker that reflects coronary plaque vulnerability. (J Am Coll Cardiol Intv 2013;6:945–54) © 2013 by the American College of Cardiology Foundation

From the *Department of Cardiovascular Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; and †Perseus Proteomics Inc., Tokyo, Japan. This study was supported in part by a JSPS Grant-in-Aid for Young Scientists (B) (24790767) (to Dr. Koga). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Pathological studies of patients with sudden cardiac death suggest that acute coronary syndromes (ACS) mostly arise as a result of thrombotic coronary occlusion after rupture of a thin-cap fibroatheroma (TCFA), is also referred to as vulnerable plaque (1). Vascular inflammation is considered to play a key a role in plaque vulnerability (2).

Although acute-phase C-reactive protein (CRP) is widely considered an indicator of systemic inflammation, the response is not specific to vascular inflammation and is triggered by many disorders that are unrelated to cardiovascular disease. Pentraxin 3 (PTX3) is a member of the pentraxin superfamily that includes CRP and serum amyloid P. High levels of PTX3 are locally expressed in vascular endothelial, smooth muscle, and vascular inflammatory cells in human atherosclerotic lesions (3,4). Plasma PTX3 is also implicated as an acute indicator and a predictor of adverse clinical outcomes of ACS (5,6). However, the association between circulating PTX3 levels and vulnerable plaque has not been directly explored.

Optical coherence tomography (OCT) is a new intravascular imaging modality that allows clear visualization of the various features of vulnerable plaques including TCFA (7). When combined with intravascular ultrasound (IVUS), OCT is currently the optimal approach to evaluating plaque characteristics. Therefore, we investigated whether systemic PTX3 levels could reflect plaque characteristics including TCFA in coronary culprit lesions assessed by OCT and IVUS.

Abbreviations and Acronyms

ACS = acute coronary syndromes
AMI = acute myocardial infarction
CRP = C-reactive protein
CSA = cross-sectional area
EEM = external elastic membrane
hs-CRP = high-sensitivity C-reaction protein
IVUS = intravascular ultrasound
OCT = optical coherence tomography
P+M = plaque plus media
PTX3 = pentraxin 3
SAP = stable angina pectoris
TCFA = thin-cap fibroatheroma
UAP = unstable angina pectoris

Methods

Study population. Between April 2009 and February 2012, 101 consecutive patients with coronary artery disease who underwent both OCT and IVUS of de novo culprit lesions in the native coronary artery at Nagasaki University Hospital were considered for inclusion in this prospective study. The exclusion criteria comprised left main lesions, ostial lesions, chronic total occlusion or severely calcified lesions, and cardiogenic shock or renal insufficiency (baseline serum creatinine >2.0 mg/dl without maintenance hemodialysis). Patients with a history of treatment for or diagnosis of carotid artery stenosis; thoracic/abdominal aortic aneurysm; or peripheral artery, collagen, malignant, infectious, and other systemic inflammatory diseases were also excluded because these conditions might affect PTX3 or CRP levels (5,8). We excluded 22 patients according to these criteria and 4 others with low-quality OCT or IVUS images. Thus, data from 75 patients with ACS (n = 28) and stable angina pectoris (SAP) (n = 47) were included in the final analysis. ACS included acute myocardial infarction (AMI) (n = 17) and unstable angina pectoris (UAP) (n = 11). We defined AMI as chest pain that persisted for >30 min, arrival at hospital within 12 h of the onset of chest pain, new ST-T wave changes or a new left bundle branch block on a 12-lead electrocardiogram and elevated cardiac markers (creatine kinase-myocardial bound or troponin T) (9). We defined UAP as angina at rest, accelerated angina, or new-onset angina without elevation of cardiac markers. We defined SAP as no change in the frequency, duration, or intensity of angina symptoms within 6 weeks before admission. This study complied with the Declaration of Helsinki with regard to investigations in humans, and the Ethics Committee of Nagasaki University Hospital approved the protocol. All participants provided written, informed consent before enrollment in the study.

Angiographic analysis. Patients were examined by quantitative coronary angiography using a CASS II system (Pie Medical Imaging, Maastricht, the Netherlands). The minimum lumen diameter, reference vessel diameter, and length of the culprit lesion were measured. Culprit lesions were identified from a combination of left ventricular wall motion abnormalities, electrocardiographic findings, scintigraphic defects, and angiographic lesion morphology.

OCT image acquisition and analysis. Patients with a Thrombolysis In Myocardial Infarction flow grade of 2 or lower underwent aspiration thrombectomy using a Thrombuster III aspiration catheter (Kaneka Medics, Tokyo, Japan) before OCT imaging. We performed OCT using the balloon occlusion method (10) and a 0.016-inch guidewire-based OCT ImagingWire catheter (LightLab Imaging Inc., Westford, Massachusetts) and a Helios occlusion balloon catheter (Goodman Co. Ltd., Nagoya, Japan). An imaging run proceeded using automated pullback at 1.0 mm/s. Acquired OCT images were analyzed using proprietary offline software from LightLab Imaging.

Two independent experienced observers who were blinded to the angiographic and clinical data analyzed the OCT images using validated criteria for plaque characterization (10). Discordance between observers was resolved by taking a consensus reading. Signal-poor lesions with unclearly delineated borders on OCT images indicated a lipid core and signal-rich homogeneous lesions overlying a lipid core indicated a fibrous cap. The thinnest part of a fibrous cap was measured 3 times, and the average was defined as fibrous cap thickness. The arc of a lipid core on cross-sectional OCT images was measured and semiquantified according to the number of involved quadrants. When a lipid core comprised >2 quadrants, it was deemed to be