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Original article

Association between serum IgG4 concentrations and the morphology of the aorta in patients who undergo cardiac computed tomography

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ABSTRACT

Background: Immunoglobulin G4 (IgG4)-related disease has been suggested to be involved in cardiovascular disorders such as chronic periaortitis. However, it remains unclear whether IgG4-related immuno-inflammation affects the subclinical stages of aortic remodeling. Here, we analyzed the relationship between serum IgG4 concentrations and the morphology of the ascending aorta.

Methods: Serum concentrations of IgG4 were measured in 322 patients who underwent 320-slice cardiac computed tomography (CT). We assessed the aortic wall area and intravascular area at the portion between the aortic valve and the bifurcation of the pulmonary artery.

Results: In total, 174 patients (54.0%) were diagnosed to have coronary artery disease (CAD) by cardiac CT. The intravascular area was significantly larger in patients with CAD than in those without (893 mm^2 vs. 811 mm^2, $p = 0.001$). The aortic wall area was slightly, but not significantly, larger in patients with CAD than in those without (183 mm^2 vs. 176 mm^2, $p = 0.051$). Serum concentrations of IgG4 were significantly higher in patients with an aortic wall area of median or greater size ($\geq$181 mm^2) than in those with a smaller area ($<$181 mm^2) (32.9 mg/dL vs. 23.1 mg/dL, $p = 0.026$). In logistic regression analysis using age, gender, and CAD as covariates, the fourth quartile of IgG4 ($\geq$55.4 mg/dL) was significantly associated with an aortic wall area of median or greater size with an odds ratio of 2.09.

Conclusions: Serum concentrations of IgG4 were found to be significantly associated with the aortic wall area. These findings collectively suggest that immuno-inflammatory processes may play a role in the subclinical stages of aortic remodeling.

Introduction

Immuno-inflammatory processes may underlie the remodeling of arteries of various sizes [1]. In addition, the activation of the immuno-inflammatory system is known to affect the development and progression of atherosclerosis [2]. Vascular remodeling represents morphological changes of the vessel wall in response to various chemokines, inducing reorganization of the vessel wall structure [3]. This affects not only the vessel diameter but also the thickness of the arterial wall.

Immunoglobulin G4 (IgG4), which is a unique antibody in both structure and function, has been recently reported to play a central role in certain immune-mediated conditions [4]. Although IgG4 is the least prevalent component of the four IgG subclasses, it may lead to overexpression of transforming growth factor β (TGF-β) via the activation of regulatory T (T_{reg}) cells, resulting in the promotion of fibrosis. Since Hamano et al. [5] first discovered the elevation of serum IgG4 concentrations and tissue infiltration of IgG4-positive plasma cells in autoimmune pancreatitis, similar clinicopathologic conditions—now designated IgG4-related disease—have been increasingly identified in a wide variety of organs.

Several vascular disorders are, at least in part, considered to possess such features of IgG4-related disease, including inflammatory abdominal aortic aneurysm, idiopathic retroperitoneal

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fibrosis, and coronary periarteritis [6–8]. For example, Matsumoto et al. [9] reported a case of multiple IgG4-related vascular lesions in which serum concentrations of IgG4 were elevated and numerous IgG4-positive plasma cells were evident within both an abdominal aortic aneurysm and tumorous lesions around the coronary artery. In addition, Kasashima et al. [10] compared IgG4-related thoracic aortic aneurysm (TAA) with IgG4-unrelated TAA, and concluded that IgG4-related TAA differed from unrelated TAA by the presence of fibrous adhesions to the surrounding tissue and histopathologically thicker aortic walls. Although a relationship between IgG4 and cardiovascular disorders has been frequently reported, it remains unclear whether IgG4-related immuno-inflammation plays a specific role in the preclinical stages of vascular remodeling. The aim of the current study, therefore, was to determine whether there is an association between serum IgG4 concentrations and the morphology of the aorta among patients who underwent cardiac computed tomography (CT).

Methods

Subjects

The study was approved by the Ethical Committee of the University of Tokyo, Tokyo, Japan. Written informed consent was obtained from all subjects. In total, 322 patients (175 men, 147 women) who gave consent and who underwent 320-slice cardiac CT between June 2010 and August 2012 were enrolled. The exclusion criteria were congenital heart disease, and previous surgery of thoracic aorta including coronary artery bypass graft surgery.

Among the 322 patients enrolled, 174 (54.0%) were diagnosed to have coronary artery disease (CAD) by cardiac CT. The medians of plasma concentrations of white blood cell (WBC) and serum concentrations of high-sensitivity C-reactive protein (hsCRP) were 5900/μL [interquartile range (IR), 4900–6900/μL] and 0.09 mg/dL (IR, 0.04–0.20 mg/dL), respectively. Body surface area (BSA) was calculated by the following equation: $BSA = 0.007184 \times (\text{body weight})^{0.425} \times (\text{height})^{0.725}$ [11]. Hypertension, dyslipidemia, and diabetes were diagnosed by reference to medical records. Smoking status was categorized as never smoker, former smoker, or current smoker; a patient was judged to be a former smoker when the period from the time of smoking cessation to cardiac CT was longer than 1 month.

Laboratory measurements

Serum concentrations of IgG4 were determined with a Behring Nephelometer II (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany) using IgG subclass BS-NIA IgG4 (Medical and Biological Laboratory Co., Ltd., Nagoya, Japan) as antibodies for serum samples. Measurements of serum IgG4 concentrations were performed in duplicate. Plasma concentrations of WBC were counted by an electric resistance method. Serum concentrations of hsCRP were measured by an immunoturbidimetric assay. Serum concentrations of creatinine were measured by an enzymatic method. The estimated glomerular filtration rate (eGFR) was calculated by the following equation: $eGFR = 194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287}$ ($\times 0.739$ if female) [12]. The median interval between cardiac CT and blood sampling was 15 days (IR, 7–46 days). During this period, there were no significant changes in medication status, such as antihypertensive drugs or antidyslipidemic drugs, among the study patients.

CT angiography and image analysis

CT scanning was performed using a 320-slice multidetector CT scanner (Aquillion ONE, Toshiba, Japan) with prospective electrocardiogram (ECG) gating axial scans. The following scanning parameters were used: detector configuration, 320 mm × 0.5 mm; rotation time, 350, 375, or 400 ms depending on heart rate; tube potential, 120 kV; and tube current, 270–550 mA depending on body weight. Patients received 20–40 mg of oral metoprolol depending on body weight 2 h before CT scanning if their resting heart rate was more than 70 beats/min. All patients received 2.5 mg of sublingual isosorbide dinitrate before imaging. Prior to CT angiography, 3-mm thick slices were acquired during a single breath hold, covering the volume between the carina and the diaphragm to measure coronary artery calcium (rotation time, 350 ms; tube potential, 120 kV; tube current, 150 mA). Image acquisition was synchronized to 40% or 75% of the R–R interval depending on heart rate. Depending on the body weight, an average of 51 ± 12 mL of contrast medium (iopamidol 370 mg I/mL, Bayer Healthcare, Berlin, Germany) was injected for 12.5–14 s. For patients undergoing CT after February 2012, we added a 30-mL saline flush after the bolus injection of contrast medium. Scanning was started with a delay according to the contrast transit time as determined previously by the bolus tracking method. Image data were transferred to a workstation for postprocessing (Ziostation, Ziosoft Inc., Redwood City, CA, USA). We measured minimal lumen diameter in the stenosis, and vessel lumen diameter immediately proximal to the stenosis. The diameter of the stenosis was subsequently calculated by dividing the minimal lumen diameter by the vessel lumen diameter. CAD was defined to be present when narrowing of the normal contrast-enhanced lumen to less than 50% was identified within any of the 13 segments (segments 1–4, 5–9, and 11–14) in accordance with the coronary classification of the American Heart Association [13]. CT angiographic images were evaluated by two experienced observers who were blind to the serum IgG4 concentrations of each patient to avoid observer bias.

Measurement of the aortic wall area and intravascular area

The aortic wall area and intravascular area of the ascending aorta were measured at the midpoint between the aortic valve and the bifurcation of the pulmonary artery using 0.5-mm slice contrast enhanced CT images for CT angiography. The cut-off value of the boundary between the aortic wall and the intravascular space was determined to be 60% of the average CT value of a region of interest (ROI), which was set in the center of intravascular space.

Statistical analysis

Data analysis was performed using Dr. SPSS II for Windows (SPSS Inc., Chicago, IL, USA). Data are expressed as mean ± standard deviation (SD) unless stated otherwise. Differences between the groups were calculated by Mann–Whitney test, *t* test, and χ^2 test. Correlations between variables were assessed by using Spearman's rank correlation coefficient. The area under the receiver operating characteristic (ROC) curve was calculated to quantify diagnostic performance. Multivariate analysis was calculated by logistic regression analysis. A p value of <0.05 was taken to be statistically significant.

Results

Baseline characteristics

The mean age of the 322 patients enrolled was 68.6 ± 9.8 years (range, 21–90 years). A total of 43 patients (13.4%) had a history of previous percutaneous coronary interventions. A summary of the clinical data of patients is provided in Table 1. Calcification of the thoracic aorta was observed in 295 patients (ascending aorta, 215 patients; aortic arch, 285 patients; thoracic descending aorta,