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Original article

Cholesterol crystal as a new feature of coronary vulnerable plaques: An optical coherence tomography study

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ABSTRACT

Background: Previous pathohistological studies demonstrated that cholesterol crystals (CCs) are frequently observed in atherosclerotic plaques, and are usually present abundantly in vulnerable plaques. However, the role of CCs in plaque destabilization, as well as their origin and composition, is unknown. Optical coherence tomography (OCT) imaging system is a high-resolution imaging device, which allows the *in vivo* identification of CCs accumulating within atherosclerotic plaques. The aim of this study was to investigate the relationship between the presence of CCs, other plaque morphologies assessed by OCT, and patients' clinical characteristics including acute coronary syndrome (ACS).

Methods and results: Preinterventional OCT images of 173 patients with either ACS or stable angina pectoris were studied. Of 173 lesions in the patients, 66 (38%) had CCs within the culprit lesion segment and 107 (62%) had non-CC lesions. Multivariate analysis revealed that low high-density lipoprotein cholesterol levels, diabetes mellitus, the presence of plaque rupture, intimal vasculature, and thrombus were independent factors associated with CCs. Moreover, the frequency of CCs increased in proportion to the accumulation of the number of components of their vulnerable plaque features within the culprit lesion segment. Compared with the plaques without thrombus, CCs were present at shallower locations in those with thrombus.

Conclusions: This study demonstrates the potential correlation between the clinical metabolic disorder and vulnerable morphological features of culprit lesions to the presence of CCs in patients with stable and unstable coronary syndromes. These observations of CCs by using *in vivo* plaque imaging could provide incremental value to OCT evaluation of atherosclerotic plaques.

Introduction

Culprit plaque morphology in patients with acute coronary syndromes (ACS) varies from thrombosis with or without plaque rupture to sudden narrowing of the lumen from intraplaque hemorrhage [1]. The early detection of vulnerable plaques is necessary to prevent ACS. For instance, a large lipid-pool, thin fibrous cap, and macrophage accumulation have been considered as vulnerable features [2]. Previous pathohistological studies demonstrated that cholesterol crystals (CCs) are frequently found in atherosclerotic plaques and are usually abundant in vulnerable plaques [3]. However, the role of CCs in plaque destabilization, as well as their origin and composition, is unknown.

Previous pathological studies by Abela et al. demonstrated that CCs could cause plaque rupture by mechanically protruding the fibrous cap and inducing thrombus formation. These studies have shown that individual CCs measured by scanning electron microscopy were 1–3 μm in diameter at the tips, 50–150 μm long, and up to 20 μm wide at the base [3]. Therefore, intravascular ultrasound images could not visualize individual CCs due to lack of spatial resolution. The optical coherence tomography (OCT) imaging system is a high-resolution imaging device that provides a maximal axial resolution of 10 μm, which allows the *in vivo* identification of not only plaque rupture, fibrous cap thickness, and

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intraluminal thrombus, but also of macrophages, intimal vasculature, and structures suggestive of CC accumulation within atherosclerotic plaques [4–7].

Thus, to date, to the best of our knowledge, few studies have investigated the relationship between the presence of CCs, other plaque morphologies assessed by OCT, and clinical characteristics in patients with stable and unstable coronary syndromes. The present study has been designed for this purpose.

Material and methods

Study population

From September 2011 to March 2015, 190 consecutive patients with either ACS or stable angina pectoris (SAP), who underwent OCT examination on a native *de novo* culprit lesion prior to percutaneous coronary intervention (PCI) at the Osaka City University, were enrolled in this study. Patients with congestive heart failure, cardiogenic shock, and who underwent prior PCI or coronary artery bypass grafting were excluded from the study. Of the 190 patients initially enrolled, 17 were excluded for technical reasons; 13 patients did not undergo OCT examination before PCI because of unsuccessful reperfusion to Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 by initial aspiration thrombectomy before imaging ($n = 5$) and failure to advance the OCT catheter to the culprit lesion ($n = 8$), and 4 patients had poor OCT images that were too low-quality to allow analysis.

Taking into account intra-patient correlations when evaluating the data, one culprit lesion was used for analysis of patients with more than 2 lesions. Thus, 173 lesions from 173 patients with either ACS or SAP, who had documented narrowing of at least 50% of the luminal diameter of a major coronary artery on coronary angiography (CAG), were examined in this study. Among the ACS patients, 112 had either acute myocardial infarction or unstable angina pectoris (UAP). Fifteen patients had acute myocardial infarction. The diagnosis was based on prolonged ischemic discomfort, characteristic electrocardiographic changes, and elevation of myocardial enzyme levels. UAP was diagnosed in 97 patients. UAP was defined either as new onset angina within 2 months after a previous ischemic event; as angina with a progressive crescendo pattern, with the angina episodes increasing in frequency and/or duration; or as angina that occurred at rest, according to Braunwald's criteria. The other SAP group included 61 patients with chest pain typical of cardiac ischemia on exertion that was clinically unchanged for >2 months. Oral aspirin (100 mg) and clopidogrel (300 mg loading dosage, 75 mg/day) or prasugrel (20 mg loading dosage, 3.75 mg/day) were administered on admission. Patients at high risk were also treated with intravenous heparin, but no patient was administered thrombolytic agents.

The following data were also collected: age, sex, and presence of risk factors [smoking and hypertension, as defined by the Joint National Committee VII; diabetes mellitus, as defined by the World Health Organization (WHO) Study Group; or dyslipidemia, as defined by the Japan Atherosclerosis Society Guidelines]. Moreover, high-density lipoprotein (HDL) cholesterol levels were categorized as either <35 mg/dL or ≥35 mg/dL, according to a previous report [8].

The study was approved by the hospital ethics committee, and informed consent was obtained from all patients before the study.

OCT image acquisition

OCT imaging was performed for the culprit vessel before intervention, after administration of 0.2 mg of intracoronary nitroglycerin. The culprit vessel was identified based on clinical, scintigram stress test, and angiographic data. In patients with TIMI flow grade ≤ 2, aspiration thrombectomy was performed using an aspiration catheter (Thrombuster II, Kaneka Medical Products, Osaka, Japan) before OCT imaging, but predilation using a balloon catheter was not performed. After reperfusion was gained with TIMI flow grade 3, OCT images were acquired using a time-domain (M2CV OCT Imaging System; LightLab Imaging, Westford, MA, USA), or a frequency-domain (C7-XR OCT Intravascular Imaging System; St Jude Medical, St Paul, MN, USA) OCT system; or an optical frequency-domain imaging (OFDI) device (Terumo OFDI system; Terumo Corporation, Tokyo, Japan). The intracoronary OCT imaging technique has been described previously [9,10].

OCT image analysis

The culprit lesion site selected for analysis was the image slice with the minimal lumen area. A 10-mm-long culprit lesion segment (5 mm proximal and 5 mm distal to the culprit lesion site) was used for the assessment of plaque morphology, in accordance with previous reports [11].

OCT image analysis was performed, using previously established criteria for OCT plaque characterization [4–7], by 2 experienced observers who were blinded to the clinical information. In the case of discordance of diagnosis between the 2 observers, a consensus diagnosis was obtained using repeated off-line readings. The presence of CCs, plaque rupture, lipid-rich plaque, thin-cap fibroatheroma (TCFA), macrophage accumulation, intimal vasculature, intracoronary thrombus, and calcification were evaluated. CC was defined as thin and linear structures with high backscattering without attenuation within the plaque. For the shallowest CC within the culprit lesion segment, the minimum depth from the lumen surface to the leading edge was also measured (Fig. 1). Plaque rupture was defined as an intimal interruption and cavity formation in the plaque. A plaque having lipids characterized by signal-poor regions with diffuse borders and present in over 90° in any of the cross-sectional images within a plaque was considered a lipid-rich plaque. TCFA was defined as a lipid-rich plaque with a fibrous cap thickness measuring ≤65 μm. Macrophage accumulation was defined as bright spots with high OCT backscattering signal variances. Intimal vasculature was defined as a black hole or a tubular structure within a plaque. Thrombus was identified as an irregular high- or low-backscattering mass protruding into the lumen. Calcification was defined as well-delineated, signal-poor regions with sharp borders. The

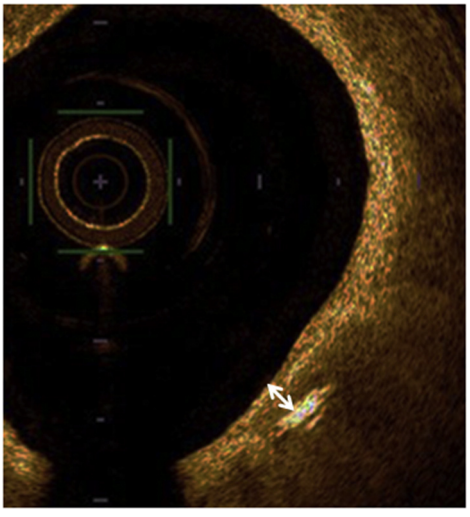

Fig. 1. Measurement of the minimum depth from the lumen surface to the leading edge for the shallowest cholesterol crystal within the culprit lesion segment.

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