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Thin-cap fibroatheroma and microchannel findings in optical coherence tomography correlate with subsequent progression of coronary atheromatous plaques

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Aims Morphological characteristics of non-significant coronary plaques (NSCPs) that develop rapid progression have not been fully elucidated. The aim of this study was to clarify the morphological characteristics of NSCPs in patients with coronary artery disease (CAD) using intravascular optical coherence tomography (OCT).

Methods and results Fifty-three consecutive CAD patients undergoing percutaneous coronary intervention were enrolled and 69 NSCPs (per cent diameter stenosis <50%) were identified on baseline angiogram. Baseline characteristics of NSCPs were evaluated by OCT, and patients were followed-up prospectively. At the second coronary angiography, the baseline OCT characteristics and plaque progression were correlated. During the 7-month follow-up period, 13 NSCPs showed angiographic progression and 56 NSCPs did not. Baseline minimum lumen diameter and diametric stenosis were similar between NSCPs with and without progression. Compared with NSCPs without progression, those with progression showed a significantly higher incidence of intimal laceration (61.5 vs. 8.9%, $P < 0.01$), microchannel (76.9 vs. 14.3%, $P < 0.01$), lipid pools (100 vs. 60.7%, $P = 0.02$), thin-cap fibroatheroma (TCFA) (76.9 vs. 14.3%, $P < 0.01$), macrophage images (61.5 vs. 14.3%, $P < 0.01$), and intraluminal thrombi (30.8 vs. 1.8%, $P < 0.01$). Univariate regression analysis showed that TCFA and microchannel images showed high correlation with subsequent luminal progression [odds ratio (OR): 20.0, $P < 0.01$ and OR: 20.0, $P < 0.01$, respectively].

Conclusion Optical coherence tomography-based complex characteristics of TCFA and microchannel were the potential predictors of subsequent progression of NSCPs in patients with CAD.

Keywords Coronary artery disease • Optical coherence tomography • Plaque morphology • Prognosis

Introduction

It is well known that acute coronary syndrome (ACS) may occur as a result of the abrupt deterioration of coronary lesions with only mild-to-moderate luminal stenosis.[1,2] Thus, it is accepted that clinical evaluation of luminal stenosis in coronary arteries, even using invasive angiography, is unable to predict the future development of ACS. Accordingly, a detailed understanding of the tissue characteristics of coronary atherosclerotic plaques is essential for identifying potentially vulnerable coronary plaques and then establishing strategies to prevent the progression and deterioration of coronary artery disease (CAD).[3]

Based on this clinical perspective, several groups have tried to elucidate the features of vulnerable coronary plaques by using intravascular ultrasound (IVUS), virtual histology-IVUS, angioscopy, and non-invasive multidetector computed tomography.[4–7] However,

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even IVUS studies have not clearly identified the specific changes in the fine morphological characteristics of plaque components or the arterial wall, or which changes predict future plaque progression and the development of ACS. This may be due partly to the limited spatial resolution (as low as 100 μm) of the IVUS technique.

Intravascular optical coherence tomography (OCT) is a newly developed imaging modality that provides clear cross-sectional images of vascular tissue with a very high spatial resolution of 10 μm.[8,9] In this study, we used intravascular OCT to evaluate the baseline morphological characteristics of a non-significant coronary plaque (NSCP) that showed subsequent rapid angiographic progression.

Methods

Patients

In Nara Medical University hospital, OCT examination were consecutively performed during percutaneous coronary intervention (PCI) when a patient fulfils the following criteria as (i) suitable coronary artery anatomy for OCT, (ii) stable patients haemodynamics, (iii) no severe co-morbid condition, (iv) no contraindications to iodinated contrast media and/or clopidogrel, and (v) informed agreement consent to study participation. From August 2008 to August 2009, 122 PCI patients were performed OCT examination. In this study, 89 patients were excluded due to diffuse multivessel stenosis (>50%) and poor quality of OCT images. Finally, 53 patients who successfully underwent both PCI and OCT examination were enrolled (male/female ratio = 42/11, average age 66.2 years).

After successful PCI, OCT examinations of three major coronary arteries were attempted. A second coronary angiographic study was performed between 6 and 9 months after PCI, or earlier if clinically indicated.

This study was approved by the Ethics Committee of Nara Medical University Hospital (#2008–20), and written informed consent was obtained from each patient before the study.

Selection of target plaques and angiographic follow-up

For the evaluation of luminal stenosis progression, we identified in each patient a focal, discrete NSCP in the non-culprit coronary arteries on coronary angiogram. Non-significant coronary plaques were defined as a plaque with a length of <10 mm and a minimal lumen diameter (MLD) of >50% of the reference vessel. Non-significant coronary plaques were chosen for follow-up analysis when (i) they were located in the proximal coronary artery segment (AHA segment 1, 2, 3, 6, 7, 11, 12, 13), (ii) suitable anatomical location for OCT evaluation with the balloon occlusion method, and (iii) did not involve major branches. On the follow-up coronary angiogram, we evaluated the changes in luminal stenosis at the pre-determined NSCP region, and angiographic progression was defined as an increase in luminal stenosis (MLD) of >0.4 mm on quantitative coronary angiography based on previous reports.[10,11]

Optical coherence tomographic data acquisition and morphological analysis

After a routine PCI procedure, an intravascular OCT device (ImageWire, LightLab Imaging, Westford, MA, USA) was inserted into target arteries through a 6 or 7 Fr guiding catheter. After intracoronary administration of nitroglycerin (0.5 mg), OCT images were recorded with the continuous infusion of Lactated Ringer's solution at 0.5 mL/s through the occlusion catheter (OBC, LightLab Imaging). The pullback speed of OCT recording was 1.0 mm/s and the frame rate was 15.6/s. OCT images were processed and analysed offline using proprietary software from LightLab Imaging. In order to ensure that identical coronary regions were examined with OCT and coronary angiography, each corresponding NSCP was marked by measuring the distance from coronary artery landmarks. Images with substantial motion artefact were removed from the assessment.

Morphological evaluation of OCT images was performed on 10 mm lengths of NSCPs (between 5 mm proximal and 5 mm distal to the site of minimal luminal area). A total of 156 consecutive OCT images for each NSCP were reviewed. To assess NSCP vulnerability, we evaluated the following 10 OCT-based characteristics: (*A*) eccentric plaque distribution, (*B*) concave lumen shape, (*C*) intimal laceration, (*D*) ruptured plaque, (*E*) microchannel, (*F*) lipid pool, (*G*) large lipid pool covered with thin fibrous cap [thin-cap fibroatheroma (TCFA)], (*H*) macrophage image, (*I*) calcium deposition, and (*J*) luminal thrombus (*Figure 1*).

The eccentricity of plaque distribution was defined as the minimal intimal thickness/maximal intimal thickness of <0.5. Luminal shape was regarded as concave if for every pair of points within the lumen, every point on the straight line segment that joined them was also within the lumen. Intimal laceration was characterized by the irregularities or disruption of the superficial intimal lining without fibrous cap ruptures.[12] Plaque rupture was defined as disrupted fibrous membrane with an underlying empty cavity. Microchannel was defined as non-signal tubuloluminal structures without a connection to the vessel lumen, recognized on more than three consecutive cross-sectional OCT images.[13] Pathohistological tissue characterization was performed according to the definitions of Kawasaki *et al.*[14] Lipid pool was defined as homogenous, diffusely bordered, signal-poor regions with overlying signal-rich bands. Thin-cap fibroatheromas were defined as a large lipid pool (one or more quadrants) covered with thin fibrous cap (cap thickness <65 μm) 0.[15,16] Calcium deposition was defined as heterogeneous, sharply delineated, signal-poor or signal-rich regions or alternating signal-poor or signal-rich regions. Macrophage image was defined as linear strong OCT images on plaque surfaces accompanied by high attenuation.[17,18] Intraluminal thrombus was identified as protruding masses attached to the arterial wall.

In order to assess the relation between baseline OCT characteristics and the clinical manifestation of NSCP progression, we divided NSCP with progression into two subgroups, as progression of NSCP with ACS presentation ($n = 3$) and progression of NSCP without clinical manifestation ($n = 10$).

OCT images were evaluated by two independent observers.

Statistical analysis

All analyses were performed using SPSS version 19 (SPSS Inc., USA). Continuous variables were compared using an unpaired Student's *t*-test or Mann–Whitney *U*-test, and data were expressed as mean ± SD or as median (25th, 75th percentile). Categorical data were evaluated using the χ^2 test. Predictors for plaque progression were investigated using univariate regression analysis. All tests were two-sided, and a *P*-value of <0.05 represented statistically significant differences.

Agreement of OCT characteristics assessment between two independent observers was quantified by Cohen's κ test of concordance. A κ-value of 0.61–0.80 indicates good agreement and 0.80–1.0 indicates excellent agreement. In this study, the mean κ-value of 10 OCT characteristic assessment was 0.882 ± 0.079.

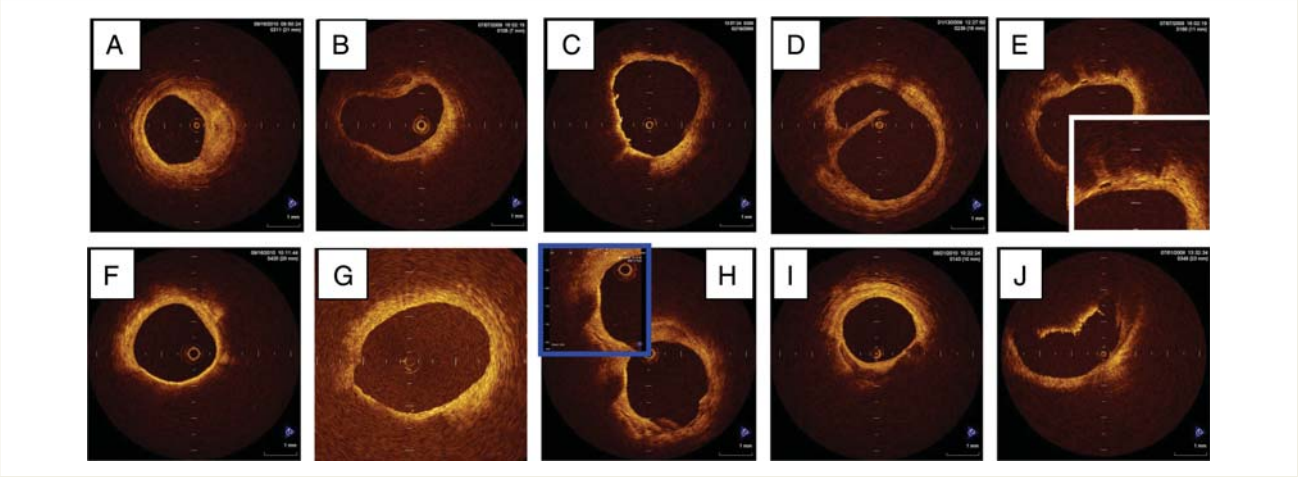

Figure 1 Ten complex optical coherence tomography-based characteristics of non-significant coronary plaques. (*A*) Eccentric plaque distribution; (*B*) concave lumen shape; (*C*) intimal laceration; (*D*) ruptured plaque; (*E*) microchannel; (*F*) lipid pool; (*G*) thin fibrous cap covering lipid pool; (*H*) macrophage image; (*I*) calcium deposition; (*J*) thrombus formation.

Table 1 Baseline patient demographics

	Progression ($n = 13$)	Non-progression ($n = 40$)	*P*-value
Age	64.5 ± 9.3	66.6 ± 9.0	0.73
M/F	8/5	33/7	0.09
BMI	25.2 ± 4.0	24.2 ± 3.6	0.30
Stable AP/UAP/AMI	4/1/8	22/4/14	0.23
Coronary risk factors			
Hypertension	9 (69%)	30 (75%)	0.99
Diabetes mellitus	7 (54%)	16 (40%)	0.94
Dyslipidaemia	9 (69%)	30 (75%)	0.99
Smoking	4 (31%)	19 (48%)	0.46
Haemodialysis	0	3 (8%)	0.99
Medication			
Aspirin	13 (100%)	40 (100%)	
Clopidogrel	13 (100 %)	40 (100%)	
Statin	13 (100 %)	34 (85%)	0.33
ACE-I/ARB	9 (69%)	35 (88%)	0.10
Mode of PCI (POBA/BMS/DES)	1/6/6	2/12/26	0.72
Follow-up period (months)	6.90 (4.38, 9.42)	6.80 (7.20, 8.40)	0.49

BMI, body mass index; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker, POBA; plain old balloon angioplasty, BMS; bare-metal stent, DES; drug-eluting stent.

Results

Baseline demographics and lipid profile

During the follow-up period, 50 patients underwent scheduled follow-up angiography, while three patients developed ACS due to progression of target NSCPs before scheduled angiography. Among 50 patients with scheduled angiography, 10 patients showed angiographic progression of the target NSCPs. Clinical parameters of enrolled patients are shown in *Table 1*. All baseline clinical parameters were similar between patients with and without plaque progression. Changes in lipid profiles are listed in *Table 2*. Baseline lipid profiles were similar between the two groups, and LDL cholesterol and L/H ratio were significantly improved during the follow-up period in both groups.

Table 2 Changes in laboratory data

	Progression		Non-progression		*P*-value		
	Baseline (A)	Follow-up (B)	Baseline (C)	Follow-up (D)	A vs. C	A vs. B	C vs. D
TC (mg/dL)	197.8 ± 54.2	156.8 ± 26.1	184.8 ± 43.3	163.0 ± 32.2	0.39	<0.01	<0.01
LDLc (mg/dL)	127.2 ± 45.1	83.1 ± 19.5	113.2 ± 35.9	89.9 ± 28.5	0.27	<0.01	<0.01
HDLc (mg/dL)	45.1 ± 8.7	48.0 ± 9.9	47.7 ± 15.0	49.0 ± 14.4	0.57	0.32	0.20
L/H ratio	2.86 ± 0.97	1.79 ± 0.58	2.60 ± 1.18	1.99 ± 1.04	0.50	<0.01	<0.01
TG (mg/dL)	118.3 ± 64.0	132.2 ± 53.6	118.8 ± 60.6	112.3 ± 51.5	0.98	0.38	0.73
HbA1c (%)	6.0 ± 0.9	6.2 ± 1.4	5.7 ± 0.7	5.7 ± 0.7	0.23	0.38	0.64
C-reactive protein (mg/dL)	0.37 ± 0.15	0.15 ± 0.16	0.46 ± 0.64	0.19 ± 0.26	0.65	0.101	0.07

TC, total cholesterol; LDLc, low-density lipoprotein cholesterol; HDLc, high-density lipoprotein cholesterol; L/H ratio, LDL/HDL ratio; TG, triglyceride.

Table 3 Comparison of quantitative coronary angiography parameters

	Progression ($n = 13$)	Non-progression ($n = 56$)	*P*-value
Location of NSCPs (LAD/Lcx/RCA)	3/3/7	16/18/22	0.34
Baseline			
Ref. diameter (mm)	2.81 ± 0.48	2.74 ± 0.67	0.74
MLD (mm)	2.06 ± 0.53	1.96 ± 0.53	0.55
Diameter stenosis (%)	28.8 ± 10.8	28.8 ± 10.9	0.99
Follow-up			
Ref. diameter (mm)	2.82 ± 0.39	2.70 ± 0.63	0.53
MLD (mm)	1.10 ± 0.60*	1.93 ± 0.52	<0.01
Diameter stenosis (%)	61.4 ± 29.3*	29.3 ± 11.6	<0.01

*$P < 0.05$, comparison with baseline values.

Finally, we identified 69 NSCPs [19 in left anterior descending, 21 in left circumflex artery, and 29 in right coronary artery (RCA)], and there was no differences in NSCP distribution in coronary arteries between the groups with or without progression (NSCP with progression: 3/3/7 and NSCP without progression: 16/18/22, $P = 0.34$). At the time of the second angiogram, 13 cases of NSCPs showed progression (3 NSCPs developed ACS and 10 NSCPs showed angiographical progression without clinical symptoms), while 56 NSCP cases did not.

Baseline and follow-up quantitative coronary angiography parameters

All patients safely underwent baseline OCT examinations and coronary angiography, and there was no complication relating to OCT examination in this study. Baseline angiographic NSCP parameters were similar between plaque cases with and without progression. Minimal lumen diameter was significantly decreased and stenosis diameter was significantly increased during the follow-up period in plaques demonstrating progression (*Table 3*).

Representative case

Figure 2 shows a representative case that developed ACS as a result of NSCP progression. An NSCP observed in the distal RCA at baseline angiography progressed significantly in 6 months (*Figure 2A* and *B*). Baseline OCT images of the NSCP revealed the presence of TCFA (*Figure 2A2*, arrowhead), microchannels (*Figure 2A2*, arrow), a large lipid pool (*Figure 2A3*), and macrophage images (*Figure 2A4*). In this case, progression of luminal stenosis was accompanied by neither TCFA rupture nor intraluminal thrombus (*Figure 2B4*), suggesting the expansion of the intraplaque component.

Optical coherence tomographic characteristics and plaque progression

Compared with NSCPs without progression, NSCPs with progression showed a significantly higher incidence of intimal laceration (61.5 vs. 8.9%, $P < 0.01$), microchannels (76.9 vs. 14.3%, $P < 0.01$), lipid pools (100 vs. 60.7%, $P = 0.02$), TCFA (76.9 vs. 14.3%, $P < 0.01$), macrophage image (61.5 vs. 14.3%, $P < 0.01$), and intraluminal thrombus (30.8 vs. 1.8%, $P < 0.01$). Univariate analysis showed that TCFA and microchannel images showed significantly high correlation with subsequent luminal progression (OR 20.0, $P < 0.01$ and OR 20.0, $P < 0.01$, respectively) (*Figure 3* and *Table 4*).

Furthermore, the frequency of pre-defined OCT characteristics observed in NSCP was compared among three groups, namely NSCP without progression, progressive NSCP without clinical manifestation, and progressive NSCP with ACS presentation (see Supplementary material online, *Table S1*). There was no difference in the frequency of 10 characteristics observed in NSCP between progressive NSCP without clinical manifestation and NSCP with ACS presentation.

Discussion

Recent clinical studies have shown that OCT is able to clearly differentiate plaque components such as intimal hyperplasia, lipid, or calcium accumulation in coronary arteries, and also visualize fine structural changes in coronary arterial walls.[19–21] These features of OCT images have been validated in histology-controlled

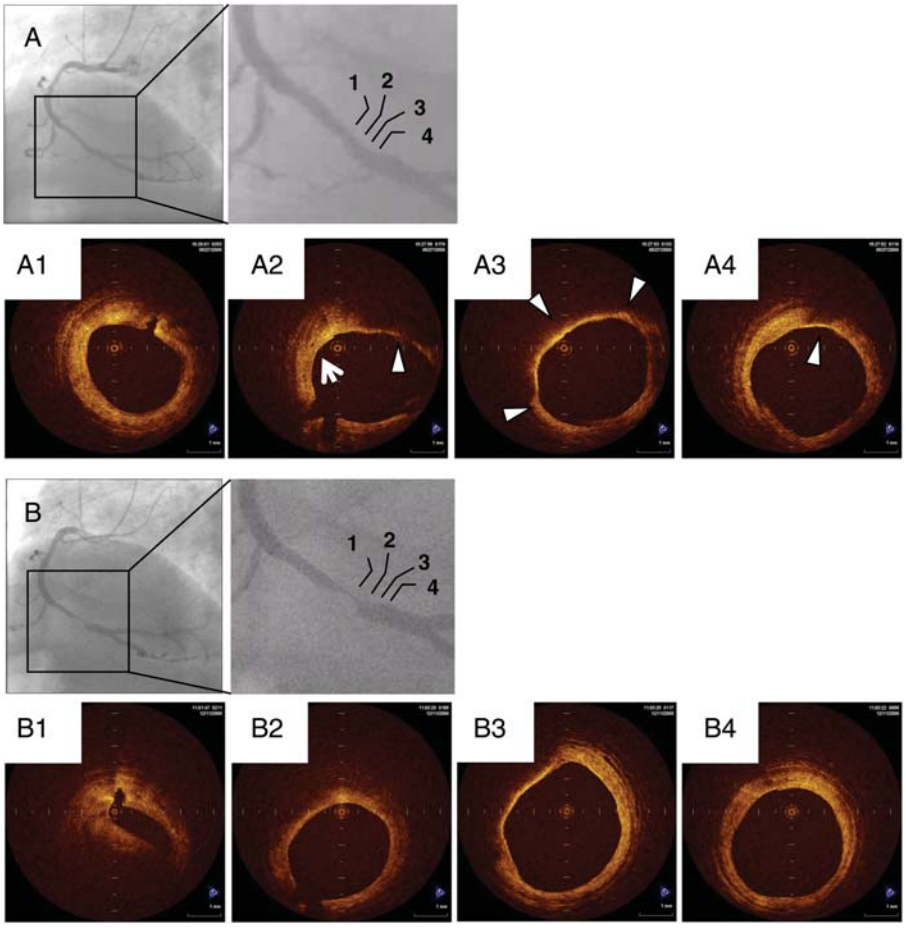

Figure 2 Angiographic and optical coherence tomographic images of representative case. (*A*) Right coronary artery at baseline angiography. (*A1–A4*) Optical coherence tomography images obtained from locations marked in (*A*) angiographic image. (*A2*) Arrowhead shows thin fibrous cap. Arrow shows microchannel in the plaque. (*A3*) Arrowheads indicate a large lipid pool. (*A4*) Arrowhead shows macrophage image. (*B*) Right coronary artery at the time of second angiography. (*B1–B4*) Optical coherence tomography images obtained from locations marked in (*B*) angiographic image.

studies, and OCT is now used to assess the vulnerability of coronary atheromatous plaques.

This prospective clinical study demonstrated, for the first time, that OCT-based complex morphological characteristics were more frequently observed in baseline NSCPs with subsequent angiographic progression of luminal stenosis and that OCT images of TCFA and microchannel are the potential predictors of future NSCP progression.

Thin-cap fibroatheroma

As one of the morphological features of vulnerable plaques, TCFAs have been extensively evaluated in both pathological and clinical studies.[2,15,16] According to studies of coronary plaques that compared patients with ACS with those with stable angina pectoris, the prevalence of TCFAs was significantly higher in the ACS group.[22,23] Furthermore, an observational study of culprit coronary plaques in patients with acute myocardial infarction reported that 73% of plaques showed disruption of fibrous caps that had presumably covered large lipid pools.[12] The above studies indicate the importance of TCFA as a feature of vulnerable plaques, but the direct relationship between TFCA and the future progression of target plaques has not yet been elucidated. This study confirmed that TCFA was not only more frequently observed in plaques with subsequent progression, but was also a powerful predictor for the future worsening of luminal stenosis. Recently, Takarada *et al.*[24] used OCT to demonstrate that intensive lipid-lowering therapy with statins increased the thickness of TCFA fibrous cap. Thin-cap fibroatheromas can be a surrogate target for the future development of anti-atherosclerotic therapy.

Intraplaque microchannels (vasa vasorum)

Neoangiogenesis in atheromatous plaques plays a pivotal role in the development and progression of coronary plaques by increasing the flow of blood, and therefore also inflammatory cells and cytokines, into the plaque. Intraplaque microvessels seem to stimulate plaque growth by supplying red blood cells, whose membranes serve as a potent source of free cholesterol.[3] Sluimer *et al.*[25]

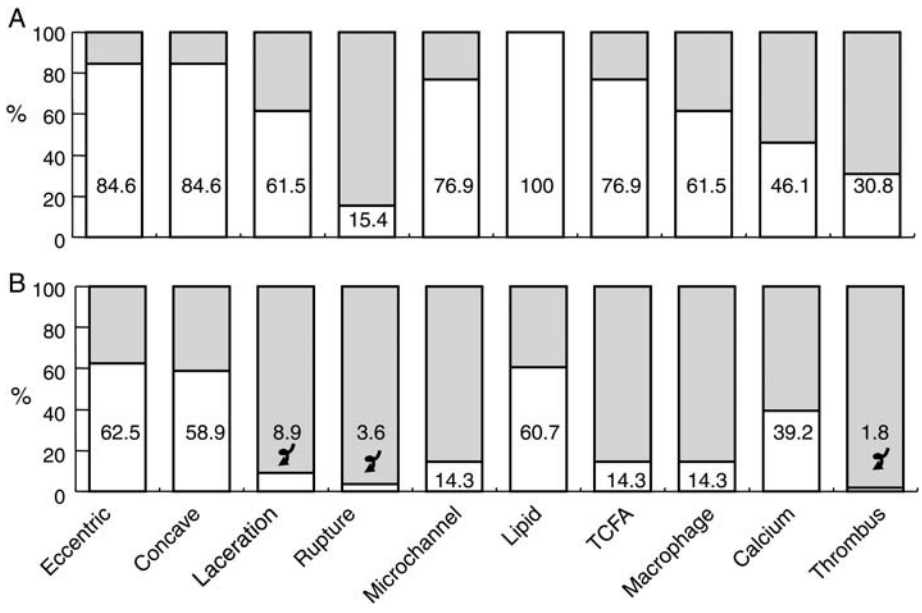

Figure 3 Prevalence of optical coherence tomographic plaque characteristics in plaques with or without progression.

Table 4 Association of 10 optical coherence tomography-based plaque characteristics and subsequent progression

	Univariate analysis	
	OR (95% CI)	***P*-value**
Eccentric	3.30 (0.73–14.4)	0.230
Concave shape	3.83 (0.85–16.7)	0.160
Intimal laceration	10.20 (2.77–37.8)	<0.001
Rupture	4.90 (0.78–31.23)	0.325
Microchannel	20.00 (4.78–82.6)	<0.001
Lipid pool	2.16 (0.57–8.06)	0.222
TCFA	20.00 (4.78–82.6)	<0.001
Macrophage	9.60 (2.60–35.6)	0.001
Calcium	1.33 (0.41–4.30)	0.890
Thrombus	12.00 (2.18–64.32)	0.002

performed a pathohistological study of coronary arteries obtained at autopsy from 28 sudden death donors. They found that microvessel density was increased in advanced plaques compared with early plaques and that microvessels were thin-walled in normal and atherosclerotic arteries. They postulated that the compromised structural integrity of the microvascular endothelium may explain the microvascular leakage responsible for rapid plaque expansion by intraplaque haemorrhage in advanced human coronary atherosclerosis.[5,25] In fact, Vorpahl *et al.*[26] demonstrated that small black holes, representing microvessels, observed in OCT images in atheromatous plaques coincided well with the pathohistological evidence of intraplaque microvessel formation in an autopsy case. More recently, Kitabata *et al.*[13] showed that microchannels detected by OCT evaluation were associated with a higher incidence of concomitant TCFAs and increased high-sensitivity C-reactive protein levels, suggesting the importance of intraplaque microchannels as a marker for plaque vulnerability. Our OCT study revealed the importance of intraplaque microchannel in subsequent plaque progression, possibly by maintaining active inflammation in the plaque as well as intraplaque rupture.

Other optical coherence tomographic characteristics

This study also demonstrated that lipid pools were observed in all NSCPs with subsequent progression, indicating the indispensable role of lipid accumulation in plaque vulnerability as well as the importance of intensive lipid-lowering therapy for the secondary prevention of CAD.

Although the correlation of macrophage with subsequent progression was relatively lower compared with TCFA and microchannel, macrophages were more frequently observed in NSCPs with progression than those without. Infiltrated macrophages in coronary plaques exert multiple biological activities, such as stimulation of neoangiogenesis and production of inflammatory cytokines and proteolytic enzymes, those directly accelerate the instability of the plaque. Although detection of macrophages by time-domain OCT systems has not yet been established, macrophage accumulation has been shown to result in high OCT signal variance and high signal attenuation due to these cells' relatively large size and their high optical contrast.[17,18,27]

Intimal erosion on its base-rich smooth muscle cells and proteoglycan layer is the second frequent cause of rapid luminal thrombus

development.[2,28] OCT image of intimal laceration, that possibly represents pathohistological erosion, was more frequently observed in plaques with progression, but the correlation with subsequent progression was relatively low. This finding may due to this study's requirement that all enrolled patients be treated with dual antiplatelet therapy during the follow-up period, which prevented platelet aggregation or thrombus formation on the erosive surface.

In contrast, the prevalence of ruptured plaques and calcium deposition were similar in plaques with and without progression. Ruptured coronary plaques were generally considered to impart a high risk of subsequent clinical events, but in this study, this finding was not a predictive factor for subsequent progression. Supporting our findings, Rioufol *et al.* demonstrated that almost 50% of cases of spontaneous coronary atherosclerotic plaque rupture without significant stenosis healed, and the degree of stenosis tended to diminish during 2 years of intensive statin and clopidogrel treatment.[29]

Early detection of vulnerable plaques is necessary for the optimal management of patients with CAD. A complete examination of the coronary arteries with OCT might provide important information about the vulnerability of coronary plaques. Furthermore, this study indicates that patients with TCFA and other complex OCT characteristics should be provided with intensive medical treatment with stain and possibly also new interventional strategies. In addition, targeting neoangiogenesis in coronary plaques seems to be an attractive future strategy for CAD treatment and prevention.

Study limitation

This study had several limitations that should be noted. First, target coronary plaques were obtained from a small study population. Although regression analysis selected microchannel and TCFA as potential predictors of NSCP progression, larger multicentre clinical investigations should be performed to confirm our results and obtain additional evidence. Especially, our finding that baseline OCT characteristics did not differ between NSCP with or without an ACS presentation should be recognized as hypothesis-generating data because only three cases developed ACS due to the progression of target coronary atheromatous plaques.

Secondly, positive remodelling at coronary plaque segments is known to be an independent predictor of subsequent cardiovascular events. Optical coherence tomography is very sensitive for tissue characterization, but its limited penetration depth makes it difficult to assess plaque features deep in coronary artery walls, as well as total plaque burden. In this study, OCT accurately identified thin fibrous caps covering lipid content, but lipid and calcium pools located deep in coronary artery walls in positively remodelled coronary segments might not be visualized by OCT. In fact, an IVUS study in a large patient population revealed that greater plaque atheroma volume is an independent predictor for the development of future cardiovascular events.[30] Co-utilization of IVUS with OCT might provide us with more precise predictive information regarding the future progression of target plaques.

Thirdly, in this study, we used a time-domain OCT that requires several complex procedures to get high-quality OCT images, and this technical complexity was one of the cause of small patient population. Furthermore, it cannot be completely ruled out that image wire and occlusion balloon might injure the vessel surface that might have contributed to subsequent plaque progression.

Fourthly, we selected target plaques with non-significant luminal stenosis. It is notable that progression of coronary plaques was seen in coronary artery segments with significant angiographic luminal stenosis as well as in those without narrowing. In fact, TCFAs with high-grade luminal stenosis (>75%) have been reported to carry a significantly higher event rate than TCFA with mild stenosis.[2] In the future, we need to develop a method of assessing the complex vascular wall characteristics of the entire coronary tree.

Conclusion

Optical coherence tomography-based complex characteristics of TCFA and microchannel were the potential predictors of subsequent progression of NSCPs in patients with CAD.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: none declared.

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