Stepwise regression of non-culprit lipid-rich plaque observed using serial near-infrared spectroscopy–intravascular ultrasound and optical coherence tomographic measurements after aggressive cholesterol-lowering treatment: a case report

Norihito Takahashi , **Tomotaka Dohi** *, **Hirohisa Endo** , and **Shinya Okazaki**

Department of Cardiovascular Biology and Medicine, Juntendo University Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Background	Lipid-rich plaques (LRP) in the non-culprit lesions (NCL) in patients with the acute coronary syndrome may trigger lesion-related, adverse cardiovascular events. Aggressive lipid-lowering therapy may stabilize LRP; however, the times of stabilization remain undefined.
Case summary	A 60-year-old man presented with unstable angina. Coronary angiography revealed a severely stenotic lesion (culprit lesion) in the left descending artery, and another non-obstructive lesion in the distal left main trunk artery. Near-infrared spectroscopy (NIRS) imaging showed LRP with a maximum lipid core burden index $(LCBI)_{4mm}$ of 422. Optical coherence tomographic (OCT) imaging showed the vulnerable plaque as a thin cap fibroatheroma with a thickness of $50\,\mu m$. We prescribed aggressive lipid-lowering treatment with a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, and serially observed this lesion for 24 months. The NIRS imaging showed that the LCBI gradually decreased over time (max $LCBI_{4mm}$ of 422, 417, 318, 265, and 106 conducted at index percutaneous coronary intervention, 3, 8, 12, and 24 months, respectively). As plaque regression and stabilization of high-risk LRP were observed, we promptly discontinued treatment with the PCSK9i inhibitor.
Discussion	During the long-term, 24-month, follow-up using serial NIRS–IVUS imaging, we observed the gradual decrease in LCBI over time, due to aggressive lipid-lowering therapy. Compared with the lowering of low-density lipoprotein cholesterol, the stabilization of vulnerable plaques may require longer times of about 2 years. Evaluation of NCL-related adverse cardiac events by serial intravascular imaging over time, using NIRS–IVUS or OCT, may be warranted in such cases.
Keywords	Case report • Near-infrared spectroscopy • Optical coherence tomography • Lipid-rich plaque • Vulnerable plaque • Non-culprit lesion

* Corresponding author. Tel: +81-3-3813-3111, Fax: +81-3-5689-0627, Email: tdohi@juntendo.ac.jp

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Learning points

- Aggressive and early lipid-lowering therapy may effectively cause lipid-rich plaque (LRP) regression; however, it may take 2 years of such treatment to decrease the lipid core.
- There is a delay of several months between the decrease of low-density lipoprotein cholesterol and the regression of LRP.
- Follow-up by near-infrared spectroscopy–intravascular ultrasound imaging such as 8 months is not sufficient to assess LRP, and longer-term follow-up such as 24 months will be needed in future large-scale studies.

Introduction

Patients with the acute coronary syndrome (ACS) face substantial risks of future adverse cardiac events, including recurrent ACS, even after revascularization of culprit lesions.[1] This risk is partly attributable to the presence of vulnerable plaques or lipid-rich plaques (LRP) in non-culprit lesions (NCLs). In the PROSPECT study, major cardiovascular events were equally attributed to the recurrences at both culprit lesions and NCLs. Additionally, the NCLs responsible for cardiovascular events were frequently angiographically mild.[2] Coronary imaging, including optical coherence tomography (OCT), intravascular ultrasound (IVUS), and near-infrared spectroscopy (NIRS), may detect vulnerable plaques, such as thin cap fibroatheromas (TCFA), larger plaque burden, and higher lipid core burden index (LCBI) that trigger lesion-related myocardial infarction.[2,3] However, the treatment strategy for vulnerable plaques in angiographically mild NCLs is not well known. Conversely, lipid-lowering therapy, with statins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, or both, reduced the risks of cardiovascular events.[4] Additionally, this treatment also reduced the plaque volumes in patients with ACS in the serial IVUS study.[5]

Here, we report the case of a patient who underwent serial assessment of vulnerable LRP in NCLs, using NIRS–IVUS and OCT, and was treated with early administration of aggressive lipid-lowering therapy with a PCSK9 inhibitor.

Case presentation

A 60-year-old man presented to our hospital with chest pain at rest. Physical examination revealed no abnormality (heart rate 70 b.p.m.; blood pressure 128/64 mmHg; respiratory rate 14 breaths/min; oxygen saturation 98% in ambient room air). The patient had hypertension and dyslipidaemia and, he was only on dietary intervention. Electrocardiography revealed sinus rhythm and inverted T wave in leads I, aVL, and V1–V4 without prior Q-wave. A chest X-ray showed no active lung lesion. Transthoracic echocardiography at the emergency department revealed an ejection fraction of almost 60% and no segmental wall motion abnormality. His laboratory tests showed normal levels of serum creatine phosphokinase at 115 (normal range 47–200) mg/dL with MB fraction at 1 (0–12) mg/dL, and normal levels of troponin-T at 0.012 (0.000–0.100) ng/mL. The patient was diagnosed with unstable angina pectoris, and he was transferred to our catheterization laboratory. We performed an urgent coronary angiogram (CAG), which showed 90% narrowing in the mid-portion of the left descending artery (LAD), and 50% narrowing in the distal left main trunk artery (LMT) (*Video 1*). We performed primary percutaneous coronary intervention (PCI) in the LAD for the culprit lesion using 2.5 mm × 30 mm Resolute Onyx (Medtronic Inc., Santa Rosa, CA, USA). Using intravascular NIRS–IVUS and OCT imaging, we evaluated the lesion with 50% narrowing in the distal LMT as an NCL. These images showed plaque vulnerability. The NIRS-IVUS images

Timeline

2017 September	• The patient was admitted to our hospital with unstable angina pectoris.
	• After primary percutaneous coronary intervention (PCI) for culprit lesion, coronary angiogram showed the presence of a non-obstructive stenotic lesion in the left main trunk artery (LMT).
	• Near-infrared spectroscopy–intravascular ultrasound (NIRS–IVUS) and optical coherence tomographic (OCT) imaging showed that the non-obstructive stenotic lesion in the LMT had lipid-rich vulnerable plaque with a thin cap and a high lipid core burden index (LCBI), which could trigger lesion-related, fatal cardiac events.
	• We treated this lesion using aggressive lipid-lowering therapy.
2017 December	• Low density lipoprotein cholesterol significantly decreased to 14 mg/dL (91% reduction from index PCI).
	• However, the NIRS–IVUS and OCT imaging findings did not show remarkable changes in non-obstructive stenotic lesion. The maximum $LCBI_{4mm}$ (max $LCBI_{4mm}$) value decreased from 422 to 417.
2018 May	• The OCT imaging showed that the fibrous cap increased in size from 50 μm to 100 μm.
	• However, the decrease in the max $LCBI_{4mm}$ value was insufficient and was limited to 318.
2019 September	• We continued serial observation of this lesion for up to 12 months and 24 months, respectively.
	• The grayscale IVUS imaging showed no remarkable changes were seen in the attenuation angle, which is an indicator of the lipid core.
	• We detected the stepwise decrease in the max $LCBI_{4mm}$ value during long-term follow-up.
	• At last follow-up, the clinical course was uneventful.
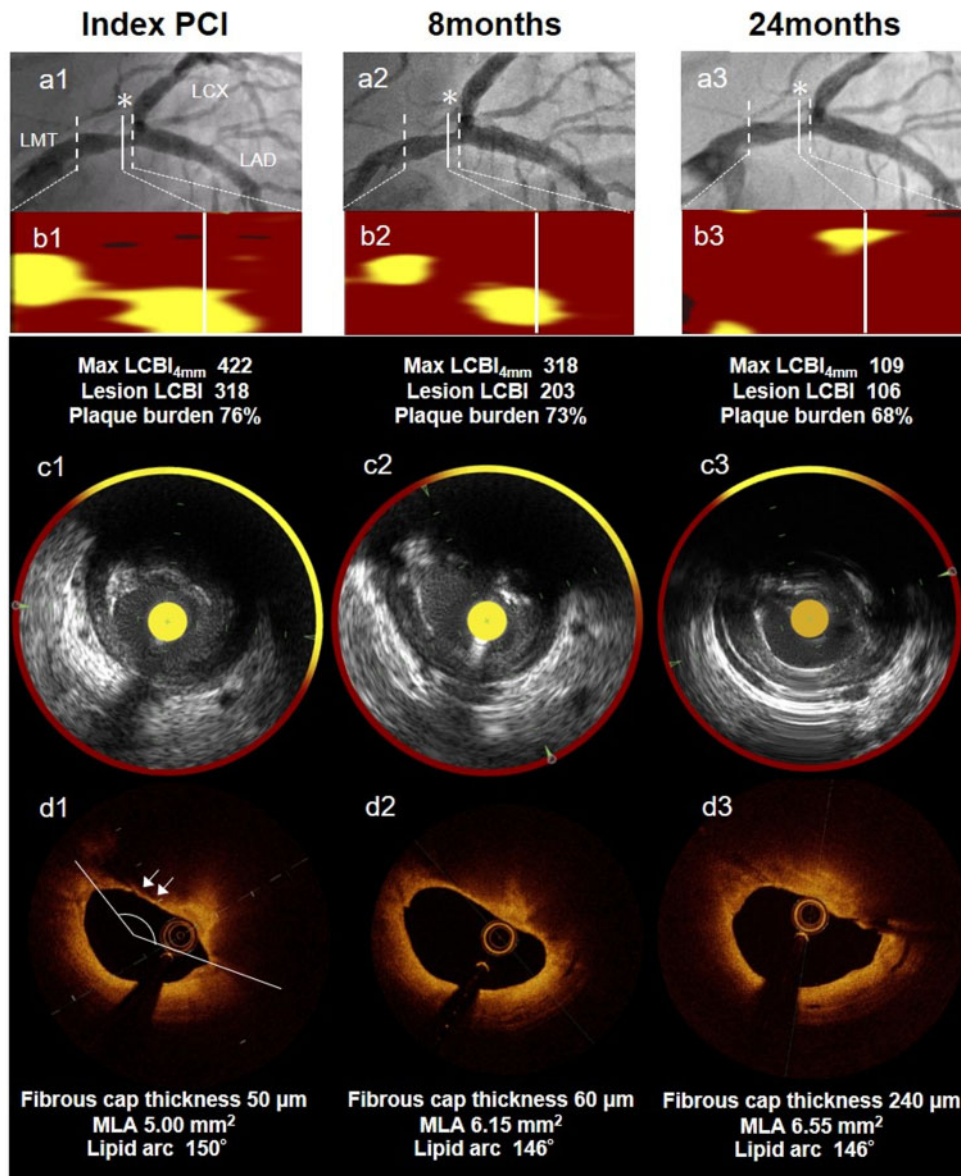
Figure 1 Case: A 60-year-old-man presenting with unstable angina pectoris. (A1–3) Coronary angiogram reveals mild stenosis in the distal portion of left main trunk artery seen as a non-culprit lesion at index primary percutaneous coronary intervention, 8 months later, and 24 months later. (B1–3) Chemogram at index percutaneous coronary intervention, 8 months later, and 24 months later. (*)minimum lumen area site. (C1–3, D1–3) Near-infrared spectroscopy-intra vascular ultrasound and optical coherence tomography images with minimum lumen area site in non-culprit lesion segment. B1–3 show that yellow pixels were significantly and gradually reduced during the follow-up duration of 24 months. Max LCBI$_{4mm}$ decreased from 422 to 106. The optical coherence tomography at index percutaneous coronary intervention detected a thin-cap fibroatheroma with a thickness of 50 μm (white arrow). This thickness increased to 240 μm at 24 months. UAP, unstable angina pectoris; LMT, left main trunk artery; PCI, percutaneous coronary intervention; OCT, optical coherence tomography; NIRS-IVUS, near-infrared spectroscopy-intra vascular ultrasound; MLA, minimum lumen area.

showed extensive amounts of lipidic materials as LRP. Maximum LCBI$_{4mm}$ was 422. The OCT showed LRP with a thin cap and thickness of 50 μm. Minimum lumen area (MLA) was 5.00 mm^2. The patient had high levels of low-density lipoprotein cholesterol (LDL-C) on admission (LDL-C 153 [70–139] mg/dL; high-density lipoprotein cholesterol 62 [45–75] mg/dL; triglycerides, 243 [30–149] mg/dL; and haemoglobin A1C 5.5 [4.6–6.2]%). We prescribed strict observation and aggressive lipid-lowering therapy using rosuvastatin (10 mg at index PCI) and alirocumab (75 mg), a PCSK9 inhibitor, every 2 weeks to rapidly reduce the levels of LDL-C, in addition to aspirin 100 mg, clopidogrel 75 mg, olmesartan 20 m, and bisoprolol 1.25 mg.
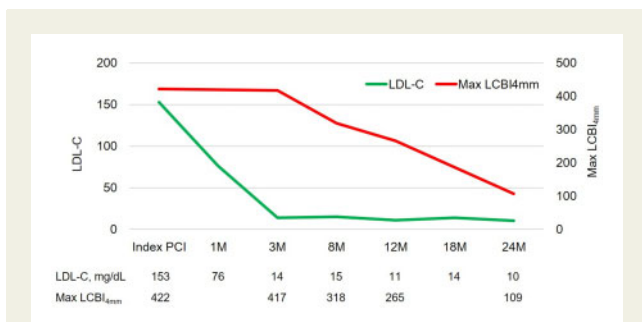
Figure 2 The line graph demonstrates that low density lipoprotein cholesterol levels decreased immediately, while the lipid core burden index value decreased gradually. LCBI, lipid core burden index; LDL-C, low density lipoprotein cholesterol.

Video 1 Coronary angiogram.

We performed serial NIRS–IVUS and OCT measurements in the distal LMT. Three months later, CAG showed a similar 50% narrowing in the distal LMT, without remarkable changes. $MaxLCBI_{4mm}$ remained high at 417. The OCT showed LRP with a thin cap of 60 μm. We continued aggressive lipid-lowering therapy and serial observation of this lesion for 24 months. The results are shown in *Figure 1*. After 24 months, we re-performed CAG, OCT, and NIRS–IVUS imaging after obtaining patient's consent. The CAG showed a similar 50% stenosis in the distal LMT. Although the OCT showed an increase in fibrous cap thickness at 240 μm, the changes in attenuation angle and low-intensity signal with irregular borders seen on the OCT and grayscale IVUS images were unremarkable. Notably, NIRS–IVUS revealed a significant reduction in LCBI (max $LCBI_{4mm}$ 106). The clinical course of the patient was uneventful. The treatment with the PCSK9 inhibitor was suspended once. The stabilized NCL will be followed up by non-invasive imaging such as coronary computed tomography angiography (CCTA).

Discussion

Patients with vulnerable plaques are at increased risk of adverse cardiovascular events. The LRP study demonstrated that the rates of non-culprit- and culprit-related major adverse cardiovascular events were similar, and 9% of patients had subsequent non-culprit events within 2 years.[3] Particularly, vulnerable plaque rupture may directly lead to death or serious cardiac outcomes, such as in cases with an LM lesion. The treatment of vulnerable plaques is important; however, the strategies remain undefined.

The PROSPECT study demonstrated that a TCFA, a plaque burden of 70% or more, and an MLA of 4.0 mm^2 or less in NCL was associated with adverse cardiac events.[2] Notably, plaque burden of 70% or more showed the strongest association. The VIVA and AtheroRemo IVUS studies confirmed these findings.[6,7] In the LRP NIRS–IVUS study, a cut-off of 400 for max $LCBI_{4mm}$ was an independent predictor for subsequent cardiac events.[3] NIRS-IVUS imaging needed to be validated for the detection of LRP. Morphologically, rupture-prone plaques are usually TCFA, including the lipid-rich necrotic core covered by a thin fibrous cap (<65 μm).[8] Cap thickness measured by OCT was associated with the prevalence of plaque
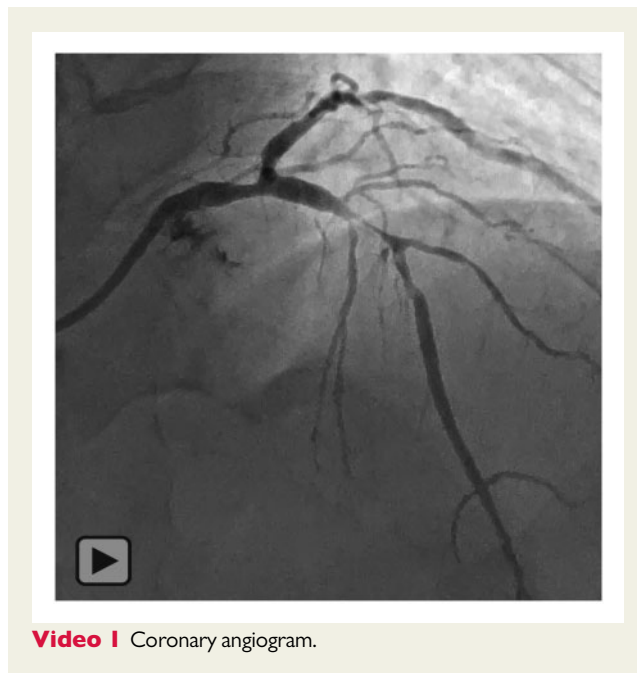
rupture.[9] In our case, LRP was detected by NIRS-IVUS (max $LCBI_{4mm}$ 400 or more) and had a large lipid arc in NCL at the index primary PCI. Additionally, our case had TCFA with a fibrous cap of 50 μm. Therefore, this NCL might have triggered subsequent serious cardiac events, such as death or serious myocardial injury. Conversely, Stone *et al.*[10] demonstrated that PCI of angiographically mild lesions with large plaque burden was safe and was associated with favourable long-term outcomes. Percutaneous coronary intervention induced the formation of a neo-cap as a barrier between the necrotic core and lumen, which stabilized the plaque, and reduced the amount of lipid core either due to plaque translation or embolization. However, in LMT, the advantages of performing revascularization of vulnerable NCLs with mild coronary stenosis remain unclear.

Plaque vulnerability is partly attributable to elevated LDL-C levels. Previous clinical trials have shown that the risk is lower among patients who receive statin therapy to lower the LDL-C levels than among those who receive a placebo.[11] In the ESTABLISH study, early high-intensity statin therapy significantly reduced the plaque volumes in patients with ACS.[5] PCSK9 inhibitors significantly reduced LDL-C levels, when administered either alone or with a statin.[12] They also reduced the risk of adverse cardiac events among such patients.[4] Recently, the PARADIGM study reported that the use of statins was associated with the decreased progression of rupture-prone plaques and plaque stability, as evident from a serial evaluation using CCTA.[13]

The patient's treatment strategy was determined according to the following reasons. First, revascularization is generally deferred in Asian patients if the MLA on IVUS MLA is ≥4.5–4.8 mm^2, because Asians generally have smaller hearts than Caucasians.[14] The patient's MLA in the LM lesion at index PCI was 5.0 mm^2, indicating that myocardial perfusion was maintained. Second, we would have had to use a stent for the bifurcation of the distal LMT to seal the vulnerable plaque; however, there was a concern of triggering critical adverse coronary events, such as stent thrombosis. Therefore, we decided to

defer revascularization and to perform strict observation with aggressive lipid-lowering therapy. In our clinical practice, non-invasive imaging such as positron emission tomography and CCTA are able to predict atheroma progression.[15,16] However, these non-invasive modalities have a low spatial resolution, making it difficult to distinguish a change in lipid core burden from fibrous cap thickness of the non-flow limiting and vulnerable rupture-prone plaque lesion in LMT. Consequently, even though this case was not in the context of a clinical trial or other research study, we selected serial evaluation by intravascular imaging, which allows for a more reliable evaluation of the risk of plaque rupture and the degree of plaque stabilization than non-invasive imaging, until the vulnerable plaque had been stabilized.

Subsequently, LDL-C levels decreased rapidly. However, compared to the rapid decrease in LDL-C, stabilizing plaque vulnerability, observed as a decreased max $LCBI_{4mm}$, needed more than 1 year (*Figure 2*). PCSK9 inhibitors are expensive drugs, and it is important to determine the duration of their use. Our case showed that LRP regression, defined by the LCBI value, requires a long term of 2 years. Therefore, long-term follow-up may be necessary when conducting large-scale studies, investigating lipid-lowering therapy and LRP regression in lesions.

Conclusions

Early aggressive lipid-lowering therapy with a PCSK9 inhibitor showed favourable outcomes for high-risk NCL LRPs in the LMT, as assessed by serial intravascular imaging, using NIRS–IVUS and OCT. As plaque stabilization of high-risk LRP may be required for at least several years, and this tends to lag behind the decrease in LDL-C levels, the serial assessment of high-risk LRP may be meaningful, in terms of treatment strategy.

Lead author biography

Norihito Takahashi received the MD degree from Juntendo University School of Medicine, Tokyo, Japan in 2013. He is medical doctor at the Department of Cardiovascular Biology and Medicine, Juntendo University Graduate School of Medicine in Japan. His research interest is mainly focused on ischemic heart disease in particular in intravascular imaging modalities.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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