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Case Report

Qualitative Improvement of a Coronary Plaque after Treatment with a Strong Statin : Observation using Virtual Histology Intravascular Ultrasound

Toru Toi, Isao Taguchi, Setsu Nishino, Michiya Kageyama, Shuichi Yoneda, Taichi Adachi, Hisashi Hasumi, Tomoaki Kanaya, Shichiro Abe, Ryuko Matsuda and Noboru Kaneko

Department of Cardiology and Pneumology, Dokkyo Medical University, Mibu, Tochigi, 321-0293 Japan

SUMMARY

Statins are used currently for treatment and prevention of coronary artery disease, but it is difficult to assess the therapeutics effects and patient responses to different statins. Virtual histology intravascular ultrasound (VH-IVUS) has been used to evaluate detailed quantitative changes in coronary plaques, and here we report a case in which marked qualitative improvement in a coronary plaque was observed using VH-IVUS after a change in treatment from a conventional statin to a strong statin.

Key Words : coronary artery disease, statin, intravascular ultrasound (IVUS)

BACKGROUND

Statin therapy is used widely for secondary prevention of formation and development of coronary plaques in patients with ischemic heart disease. A meta-analysis has shown that 86 % of patients with coronary disease had less than 70 % stenosis before onset of acute myocardial infarction[1]. This indicates that regression of coronary plaque alone does not account for the prevention of acute myocardial infarction. Intravascular ultrasound (IVUS) has been developed to evaluate the nature of coronary plaques, and spectral analysis of IVUS radiofrequency (RF) data allows quantitative and qualitative assessments of the composition of a coronary plaque in vivo[2～5]. This approach has shown that plaques have four histopathological elements : fibrous, fibro-fatty, and dense calcium components, and a necrotic core[6]. Human coronary plaque composition in vivo can now be visualized using virtual histology (VH) to generate a color-coded map[7]. In the present case, we observed changes in VH data with serial IVUS examinations and found a marked qualitative improvement in a coronary plaque in a patient with coronary artery disease who was treated with a conventional statin for 6 months and then a strong statin for a further month.

CASE REPORT

A 72-year-old woman with hypertension, hyperlipidemia and diabetes was admitted to our hospital and diagnosed with acute coronary syndrome (ACS). Following coronary angiography (CAG), percutaneous coronary intervention (PCI) was performed on the left anterior descending artery (LAD). A stent was placed under distal protection.

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Reprint requests to : Isao Taguchi, MD.
Department of Cardiology and Pneumology, Dokkyo Medical University, Mibu, Tochigi 321-0293 Japan.

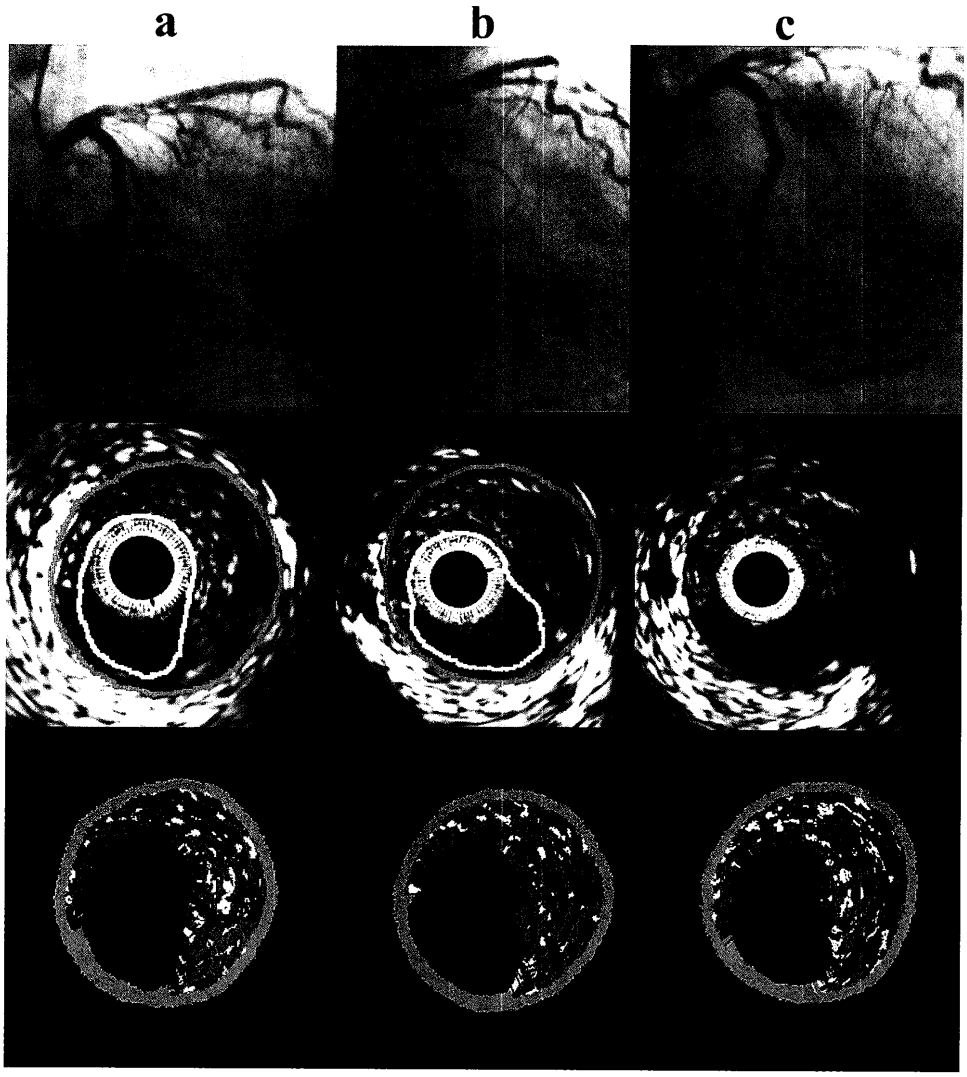

Fig. 1 Serial LCX CAG findings, gray scale IVUS and VH-IVUS color images. Arrows indicate IVUS observation sites. No changes in the rate of coronary artery stenosis or plaque burden are apparent on gray scale IVUS. The areas indicated with red and yellow are the external elastic membrane and the lumen, respectively. VH-IVUS showed that the necrotic core (red) increased during 6 months of conventional statin therapy (5 February 2007), but decreased after treatment with a strong statin (2 March 2007), while the extent of fibrosis (green) increased.

After 6 months, repeat CAG showed that the LAD stent was patent and demonstrated 50% stenosis of the left circumflex artery (LCX) (Fig.1a). IVUS was performed using automated continuous pullback (0.5 mm/s) after injection of 2.5 mg isosorbide dinitrate into the LCX. After confirming that pullback could be performed consistently, an operator confirmed the presence of the coronary artery lesion between two identified branches so that the observation range was the same. IVUS RF data were obtained using a 20-MHz 2.9F phased-array IVUS catheter (Eagle Eye® Gold, Volcano, Rancho Cordova, CA, USA) and a dedicated console (IVG3, Volcano). Quantitative and qualitative data analysis was performed using VH-IVUS Version 1.3j software (Volcano). IVUS volume analysis of the plaque lesion was corrected for the length of the coronary lesion (mm^3/cm), and the lumen volume, external elastic membrane (EEM) volume, and plaque volume were determined. The plaque burden (%) was calculated as follows : (EEM volume-lumen volume) /EEM volume. For qualitative analysis, the plaque was classified into four elements : fibrous, fibro-fatty, and

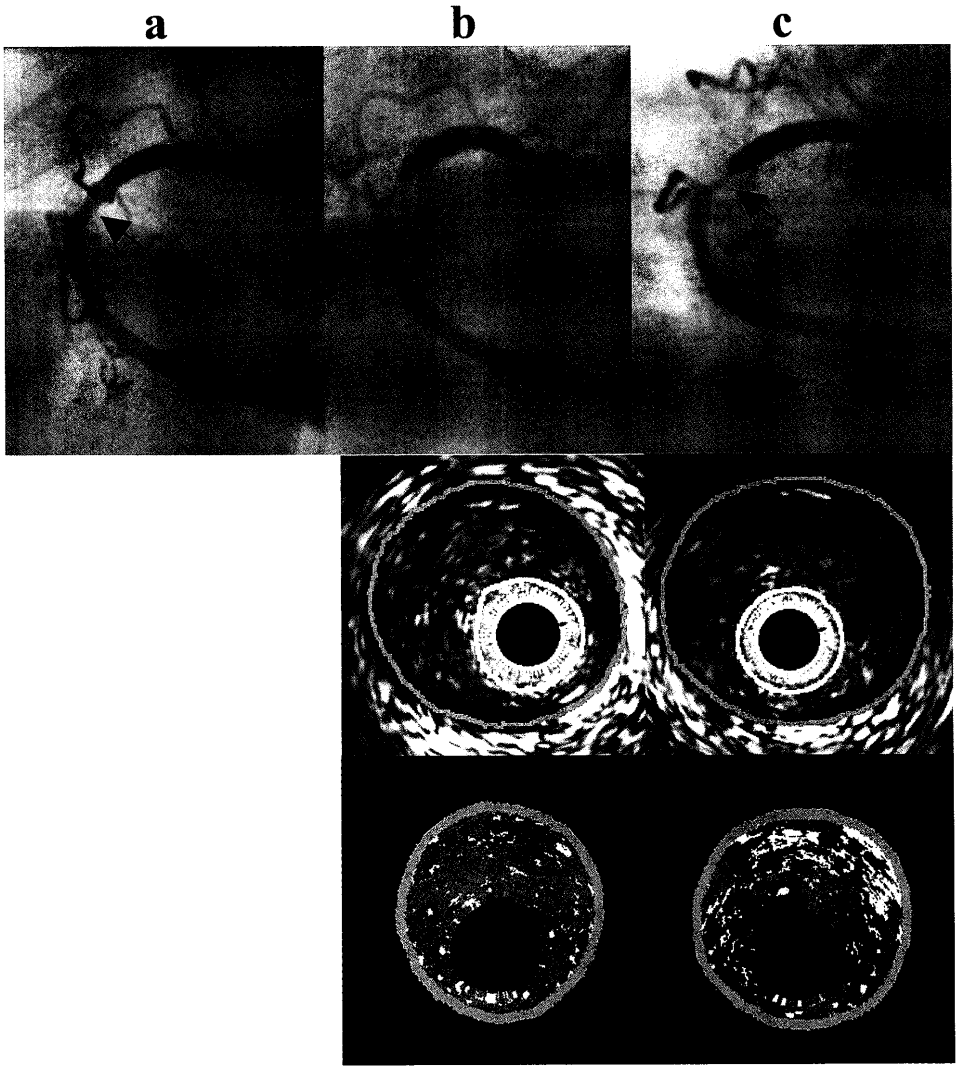

Fig. 2 Serial RCA CAG findings, gray scale IVUS, and VH-IVUS color images. Arrows indicate IVUS observation sites. There was no change in the rate of coronary artery stenosis or plaque burden. The areas indicated with red and yellow are the external elastic membrane and the lumen, respectively. VH-IVUS demonstrated a marked increase in fibrosis (green) and a marked decrease in the necrotic core (red) during one month of therapy with a strong statin.

dense calcium components, and a necrotic core, which appeared as green, light-green, white and red, respectively, in images. The amount of each element of the plaque was expressed as a percentage of the total plaque volume. Right coronary artery (RCA) IVUS was not performed at this time because CAG showed 25 % stenosis of the lesion (Fig. 2a).

Total cholesterol was 225 mg/dl and LDL-C was 152 mg/dl at the time treatment with 5 mg plavastatin was started. Several months later, the total cholesterol and LDL-C levels had increased to 249 and 160 mg/dl, respectively (Table 1). We strongly recommended a change to a stronger statin, but plavastatin was continued with diet and exercise therapy at the patient's request.

Follow-up CAG after 6 months (05 February 2007) revealed no stent restenosis in the LAD and no progression of LCX stenosis (50 %) (Fig. 1b), but a new lesion (90 % stenosis) had appeared in the RCA (Fig. 2b). We re-examined the LCX and RCA lesions by IVUS. To detect the previous coronary culprit lesion, the surrounding conditions, such as calcification and distance from the marking branch, were confirmed and IVUS pullback imaging was performed. In the

Table 1 Plasma Lipid Changes

Date	6. 22. 2006	7. 5. 2006 (1st IVUS)	11. 9. 2006	2. 5. 2007 (2nd IVUS)	3. 2. 2007 (3rd IVUS)	3. 29. 2007
Total cholesterol, mg/dl	225	184	249	174	97	159
LDL-C, mg/dl	152	112	160	108	48	78
HDL-C, mg/dl	32	37	53	48	38	49
Triglycerides, mg/dl	207	176	181	88	53	158

IVUS, intravascular ultrasound, LDL-C, low-density lipoprotein cholesterol, HDL-C, high-density lipoprotein cholesterol.

Table 2 VH-IVUS analysis of the left circumflex coronary artery

Date	7. 6. 2006	2. 5. 2007	3. 5. 2007
IVUS volumetric analysis			
Lumen volume, mm^3/cm	73.9	67.3	62.3
EEM volume, mm^3/cm	159.7	158.9	167.3
Plaque volume, mm^3/cm	85.8	91.6	104.9
% Plaque burden	54	58	63
VH analysis, color-coded mapping method			
Fibrosis, % (green area)	55	50	66
Fibro-fatty, % (light-green area)	5	5	5
Dense calcium, % (white area)	7	7	3
Necrotic core, % (red area)	32	39	27

VH IVUS, virtual histology intravascular ultrasound, EEM, external elastic membrane. After treatment with a strong statin (5 March, 2007), the lumen volume decreased and plaque volume and burden increased, but the extent of the necrotic core decreased and fibrosis increased, suggesting a qualitative improvement.

Table 3 VH-IVUS analysis of the right coronary artery

Date	2. 5. 2007	3. 5. 2007
IVUS volumetric analysis		
Lumen volume, mm^3/cm	55.6	44.6
EEM volume, mm^3/cm	198.4	213.2
Plaque volume, mm^3/cm	142.8	168.2
% Plaque burden	72	79
VH analysis, color-coded mapping method		
Fibrosis, % (green area)	57	91
Fibro-fatty, % (light green area)	6	6
Dense calcium, % (white area)	5	2
Necrotic core, % (red area)	33	2

IVUS, virtual histology intravascular ultrasound, EEM, external elastic membrane. As seen with the LCX, after treatment with a strong statin, the lumen volume decreased and the plaque volume and burden increased, but the extent of the necrotic core decreased dramatically and fibrosis markedly increased, suggesting a qualitative improvement.

LCX lesion (Fig. 1, arrow in CAG) the lumen volume had decreased and the plaque volume and burden had increased (Table 2). In the RCA lesion the lumen volume was small and the plaque burden was 72% (Table 3). VH-IVUS indicated a decrease in fibrosis (green) and a marked increase in the necrotic core (red) in the LCX after 6 months, and a rich necrotic core (red) in the RCA (Fig. 1b, 2b lower panel).

Because of the progression of coronary stenosis, plavastatin was changed to 2 mg pitavastatin with 1800 mg ethyl icosapentate (EPA). The period of the hospital stay was prolonged due to urinary tract infection, but further examination showed a marked decrease in the LDL-C level to 48 mg/dl (Table 1). After one month of administration of the strong statin, we obtained informed consent, performed CAG for PCI in the RCA lesion (90 % stenosis) and placed a stent (Vision stent 4.0 × 18 mm) (Fig. 2c). Prior to this procedure, IVUS showed that the lumen volume had decreased and the plaque volume and burden had slightly increased, while VH-IVUS showed that the extent of fibrosis (green) had increased in the LCX and the RCA, and the necrotic core (red) had decreased (Fig. 1c, 2c middle and lower panel). Greater changes were observed in the RCA. The patient was discharged without complication and with no alteration in concomitant antihypertensive, antiplatelet or oral antidiabetic drugs, or nicorandil. In the observation period, LDL-C was 78 mg/dl (Table 1) one month after discharge.

DISCUSSION

In this case, we were able to observe stabilization of coronary plaques in the LCX and RCA using VH-IVUS. In the LCX, the plaque histology worsened over 6 months of conventional statin therapy, but showed a tendency to improve after administration of a strong statin for a subsequent month. In the RCA, a rapid increase in coronary stenosis and destabilization of the plaque were observed with conventional statin therapy, with histological stabilization of the plaque upon administration of the strong statin.

Secondary prevention of ischemic heart disease has been demonstrated in several large-scale studies using conventional statins[8~10]. Subsequently, stronger statins have been developed that are able to reduce low-density lipoprotein cholesterol (LDL-C) levels to a greater extent. Comparison of the effects of newer and older statins in patients with ACS have shown greater inhibition of coronary events in those receiving a strong statin[11]. However, regression of a coronary plaque does not account for prevention of acute myocardial infarction or for secondary prevention of myocardial infarction, and the effects of statins recommended in guidelines for arteriosclerosis prevention differ among individual patients. Furthermore, a relationship between the necrotic core and ACS has been described[12], and ultrasonic attenuation assessed by IVUS has been demonstrated to be predictive for restenosis after PCI[13]. Thus, it is important to evaluate the quantity or extent and the quality of coronary plaques, and plaque regression has been reported after long-term treatment with strong statins[14~16].

In our case, relatively short-term treatment with a strong statin and EPA led to histological stabilization of a coronary plaque. The fibrous component (green in VH-IVUS images) consists of a mass of collagen fibers with slight lipid deposition, and is considered to have a relatively stable composition. The necrotic core (red in VH-IVUS) has a high lipid content, contains many necrotic and lysed cells, is associated with a foamy cell residue, and is generally considered to be structurally unstable. In patients receiving lipid-lowering therapy, Takano et al. have reported changes in the color and morphology of coronary plaques after stabilization, using VH-IVUS[17]. Only short-term strong statin therapy with EPA was used in the present case, but the effects on the RCA lesion were greater. This may be because this lesion was "younger" or "fresher" than that in the LCX, or may be due to the location of each lesion, the difference in blood flow to the coronary plaques, or a different inherent sensitivity for the statin and EPA. Recently it has been reported that the therapy of EPA prevents the coronary events in Japanese hypercholestaemic patients[18]. Not only strong statin but also EPA may be effective on the lesion of coronary plaque. It is likely that histological stabilization precedes coronary plaque regression, which has been demonstrated using markers such as leukocyte telomere length[19], adiponectin[20] and oxidized low-density lipoprotein[21]. Comprehensive assessment of several factors is required for prevention of coronary heart disease caused by arteriosclerosis, and evaluation and management of these factors may provide new options for treatment. Improvement requires both restoration of patency of the coronary artery by PCI and therapeutic reduction of atherosclerotic lesions of the artery.

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