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Case Report

A case of repetitive acute coronary syndrome in a patient with familial hypercholesterolemia

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ABSTRACT

The low-density lipoprotein-cholesterol (LDL-C) level of a 60-year-old woman diagnosed with acute coronary syndrome (ACS) was 212 mg/dL. She was suspected of having familial hypercholesterolemia, therefore, administration of a proprotein convertase subtilisin-kexin type 9 (PCSK9) antibody in addition to atorvastatin plus ezetimibe was initiated, reducing her LDL-C level to 42 mg/dL. Nine months after initial ACS, the PCSK9 antibody was discontinued. Six months after the iturruption, she relapsed with ACS, and neoatherosclerosis progression was confirmed via intravascular ultrasound. Then, the PCSK9 antibody was reintroduced. Disruption of a PCSK9 may be associated with the progression and destabilization of neoatherosclerosis.

<**Learning objective:** Administration of a proprotein convertase subtilisin-kexin type 9 (PCSK9) antibody in addition to statin decreases low-density lipoprotein-cholesterol level and is effective in suppressing cardiovascular events, the effect on neoatherosclerosis after coronary artery stent deployment is not clear. We experienced an interesting reccurent ACS case with familial hypercholesterolemia, and reported the possibility that PCSK9 antibody disruption might contribute to destabilization of neoatherosclerosis after coronary stenting utilizing intravascular ultrasound.>

Introduction

Patients with familial hypercholesterolemia (FH) show a remarkable increase in low-density lipoprotein-cholesterol (LDL-C) compared with hypercholesterolemia cases without a genetic background [1].Therefore, the progression of arteriosclerosis is fast, and early-onset coronary atherosclerosis is present; thus, aggressive lipid-lowering therapy is necessary. However, it is often difficult for patients with FH to achieve reduced LDL-C levels to the target level specified by guidelines with oral medicine alone. Proprotein convertase subtilisin-kexin type 9 (PCSK9) antibodies have a marked LDL-C-lowering effect [2,3], and it is expected to be a useful drug for lipid-lowering therapy for FH that is not well controlled by conventional treatment.

Case presentation

A 60-year-old woman was first hospitalized in our hospital with a diagnosis of acute coronary syndrome (ACS). She had a prior history of hypertension, dyslipidemia and hyperuricemia, which were treated with telmisartan 40 mg/daily, atorvastatin 10 mg/daily and febuxostat 20 mg/daily, respectively. She had no smoking history. The patient's daughter was also being treated for

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dyslipidemia. The patient had chest pain with slight exercise for a few days prior to admission. At the general hospital, a 12-lead electrocardiogram (ECG) obtained after exercise revealed serious ST-segment depressions in the , , aVF and V5-V6 leads with chest pain (Fig. 1(A)). She was suspected to have ischemic heart disease and was transferred to our hospital. On admission, her blood pressure was 164/97 mmHg, heart rate was 68 bpm and regular, and respiratory rate was 16 breaths per minute. Her body height was 148 cm, body weight was 55.2 kg and body mass index was 25.2 kg/m2. On the physical examination, the results of cardiac and pulmonary auscultation were normal. The 12-lead ECG showed inverted T waves in the V2-V5 leads (Fig. 1(B)). In a blood analysis, aspartate aminotransferase was 38 U/L, alanine aminotransferase was 38 U/L, lactate dehydrogenase was 247 U/L, creatine kinase was 92 U/L, creatine kinase MB was 12 U/L, troponin T level was 0.022 ng/mL, and casual blood glucose and hemoglobin A1c (US National Glycohemoglobin Standardization Program) were 100 mg/dL and 6.1%, respectively. Considering these findings, she was diagnosed with unstable angina pectoris and underwent emergency coronary angiography (CAG). CAG revealed 99% stenosis of her proximal left anterior descending coronary artery (LAD) (Fig. 2(A)). The culprit lesion was identified as a LAD lesion, and percutaneous coronary intervention (PCI) was performed. In an intravascular ultrasound (IVUS), lipid plaque with echo-attenuation was recognized in the culprit lesion (A and B in Table 1). Therefore, a 2.75 × 14-mm zotarolimus-eluting stent (Resolute Integrity™, Medtronic, Minneapolis, MN, USA) was implanted in the LAD, generating excellent results on both angiography (Fig. 2(B)) and IVUS (C and D in Table 1), without stent edge dissection or incomplete dilatation. At the time of the PCI, a loading regimen of 200 mg aspirin and 20 mg prasugrel was administered, and after placing the Resolute Integrity™ stent, a dual anti-platelet therapy (DAPT), a normal regimen of 100 mg aspirin and 3.75 mg prasugrel daily were initiated. In a fasting blood examination, the levels of LDL-C, high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were 186, 64 and 103 mg/dL, respectively. These levels were measured using the direct method according to the protocol supplied by the manufacturer. Although she was taking atorvastatin 10 mg daily, the level of LDL-C was markedly high. According to her home doctor, the LDL-C level while untreated was 212 mg/dL. Furthermore, an Achilles tendon xanthoma (right 9 mm, left 9.5 mm) was confirmed, and she was diagnosed with FH according to Japanese [4] and Western [5,6] diagnostic criteria. Lipid management combined with atorvastatin 10 mg and ezetimibe 10 mg did not achieve the target lipid levels specified by the guidelines [4]; thus, alirocumab

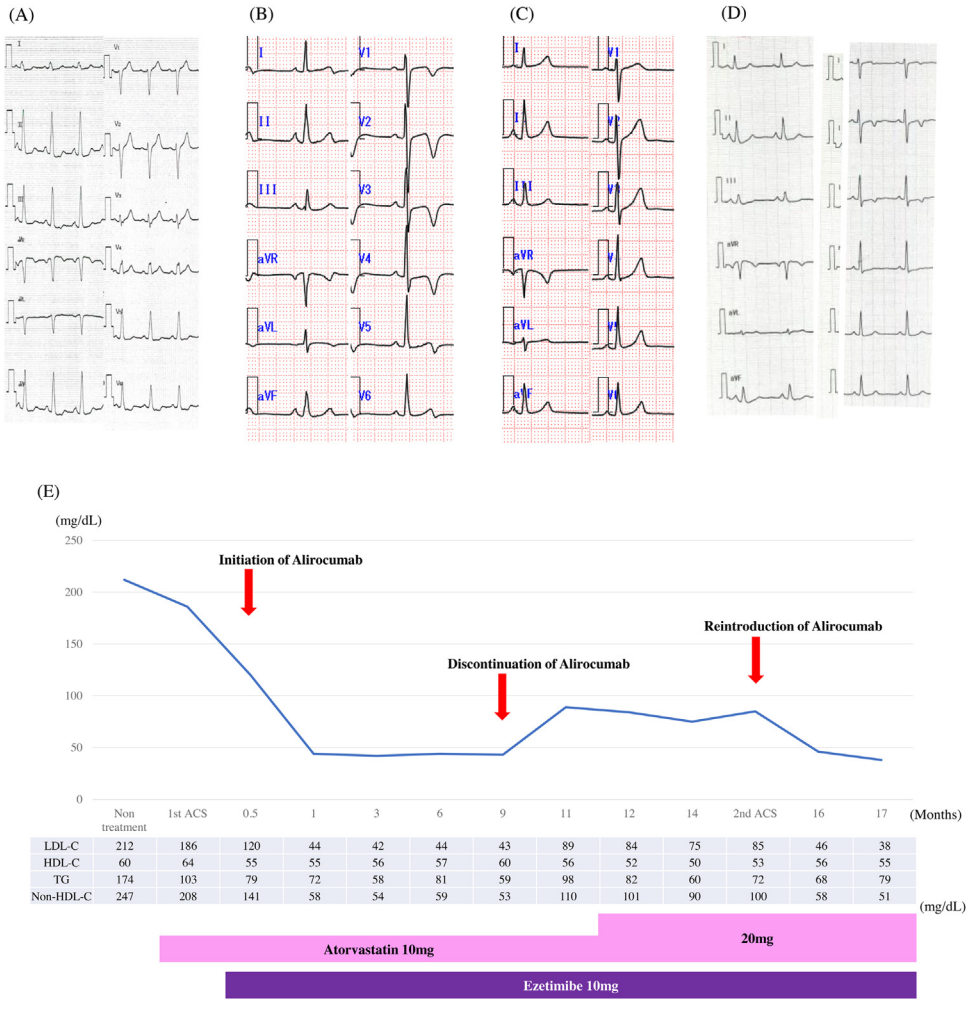


Fig. 1. (A) 12-lead electrocardiograms after the exercise test at the general hospital. (B) 12-lead electrocardiograms on first admission for ACS. (C) 12-lead electrocardiograms 9 months after PCI. (D) 12-lead electrocardiograms on second admission for ACS. (E) Clinical courses of the LDL cholesterol concentration levels (upper panel) and detailed serial changes in the lipid parameters (lower panel).

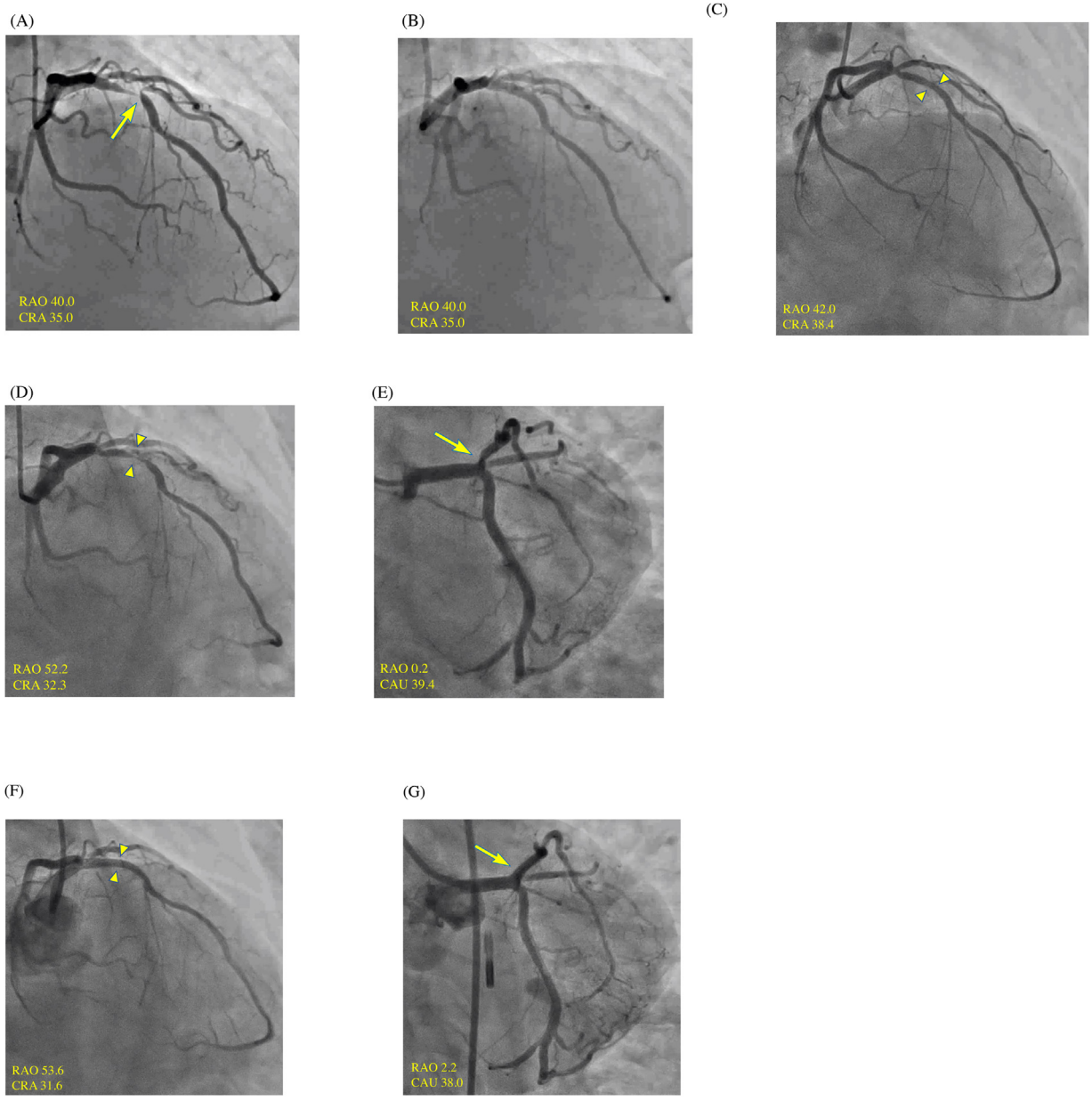


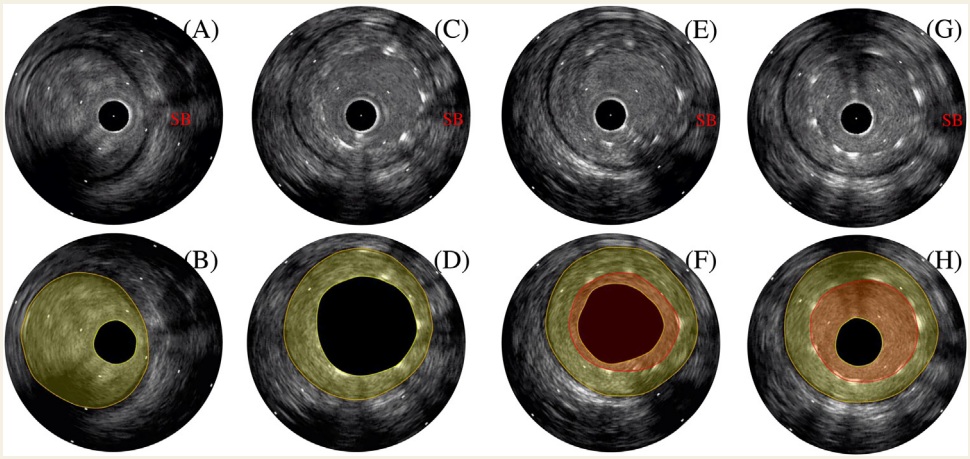
Fig. 2. Coronary angiography (CAG). (A) 99% stenosis of the proximal left anterior descending coronary artery (LAD [arrow]). RAO: right anterior oblique view, CRA: cranial view. Each number represents an angle (°). (B) Post-stent deployment, with excellent results. (C) Nine months after initial PCI. (D) 99% stenosis of the LAD stent site at reccurence (arrowhead). (E) 75% stenosis of the LAD ostium (arrow). CAU: caudal view. (F) Post-drug-coated balloon, with excellent results (arrowhead). (G) Post-stent deployment, with excellent results (arrow).

(Praluent™, Sanofi Corporation, Tokyo, Japan), a human monoclonal antibody to PCSK9, was introduced. After one month, the levels of LDL-C, HDL-C and TG had improved to 44, 55 and 72 mg/dL, respectively, with atorvastatin 10 mg daily, ezetimibe 10 mg daily and alirocumab 75 mg administered percutaneously every 2 weeks. Detailed serial changes in the lipid parameters are shown in Fig. 1E. The time of lipid measurement was just before alirocumab injection. The PCSK9 antibody was initiated to achieve an LDL-C level less than 70 mg/dL. No further stent thrombosis or stent restenosis occurred during the follow-up period. The 12-lead ECG improved to the normal range (Fig. 1C). A planned follow-up CAG was performed nine months after PCI. The CAG revealed no stent restenosis of the LAD lesion (Fig. 2C). In the IVUS, a thin neointima was recognized inside the stent (E and F in Table 1). Then, DAPT was switched to antiplatelet therapy of 100 mg aspirin daily. Alirocumab was discontinued due to financial reasons; however, the level of LDL-C was over 70 mg/dL, and increasing the amount of atorvastatin to 20 mg did not achieve the target level of guidelines.

Six months after discontinuation of alirocumab, she visited our hospital because she had chest pain with slight exercise for a few days. During the hospital visit, her chest pain disappeared. Although no cardiac markers were elevated, the 12-lead ECG showed new inverted T waves in the V1-V4 leads (Fig. 1D). Considering these findings, she was diagnosed with unstable angina pectoris and underwent emergent CAG. The CAG revealed 99% stenosis of the LAD stent site (Fig. 2D) and 75% stenosis of the LAD ostium (Fig. 2E). On IVUS, low echoic neoatherosclerosis in the layer of the neointima was recognized in the in-stent restenosis (ISR) site (G and H in Table 1). Therefore, a 3.0 × 20-mm

Table 1 Measurement Results Obtained by Intravascular Ultrasounds (IVUSs). Lower panel indicates intravascular ultrasound (IVUS) images. The yellow zones indicate plaque area. The red zones indicate neoatherosclerosis area. ACS: acute coronary syndrome, PCI: percutaneous coronary intervention, SB: septal branch.

Status	1st ACS (pre-PCI)	1st ACS (post-PCI)	9 months follow-up	2nd ACS (pre-PCI)
Lumen area (mm^2)	1.20	6.26	3.90	1.32
Vessel area (mm^2)	10.65	13.31	13.57	13.43
Plaque area (mm^2)	9.45	7.04	9.67	12.11
Stent area (mm^2)		6.26	6.55	6.19



Drug-Coated Balloon (SeQuent Please™, NIPRO Corporation, Osaka, Japan) was used at the ISR site, and a 3.5 × 12-mm sirolimus-eluting stent (Ultimaster™, Terumo Corporation, Tokyo, Japan) was additionally implanted from the left main trunk to the LAD stent site, generating excellent results on both angiography (Fig. 2F and G) and IVUS, without stent edge dissection or incomplete dilatation. The detailed measurement results from IVUS are shown in Table 1. In the emergency department, the levels of LDL-C, HDL-C and TG were 85, 53 and 72 mg/dL, respectively. An LDL-C level less than 70 mg/dL was not achieved; therefore, alirocumab was reintroduced. She was discharged from our hospital without complications after PCI. The patient provided consent for publication.

Discussion

In this case, the level of LDL-C achieved a value under 70 mg/dL during alirocumab administration. However, the level of LDL did not decrease to under 70 mg/dL despite an increase in the statin dose after discontinuation of alirocumab; unfortunately, ACS occurred six months later. In intravascular studies, progression of neoatherosclerosis was recognized at the ISR site, compared with 9 month after initial PCI. The main cause of ACS was considered to be failure to achieve target LDL-C levels according to guidelines because of discontinuation of PCSK9 antibody. It was thought that neoatherosclerosis, which was suppressed by PCSK9 antibody, increased destabilization due to discontinuation of PCSK9 antibody. We have already reported a case of plaque regression by PCSK9 antibody [7]; thus, the clinical course of this case can be interpreted as a natural result.

The median stent duration with neoatherosclerosis was shorter in DES than BMS(DES, 420 days [inter- quartile range [IQR]: 361–683 days]; BMS, 2160 days [IQR: 1800–2880 days] [8], it is consistent with the timing of second ACS. In the present case, adequate neointimal suppression was confirmed from 9 months follow up IVUS, it is suggested that the change of treatment might be associated with subsequent progression of neoatherosclerosis. The possibility of stent thrombosis could not be denied because of single anti-platelet therapy status. However, there were no findings suggesting the presence of thrombus in the stent in the evaluation using IVUS image before pre-dilatation. Rather, the IVUS image exhibited that the tissue in the stent presents mixed plaques containing lipid cores, which causes destabilization of the lesion in addition to the growth of neoatherosclerosis, and although it was difficult to observe in detail for IVUS, the second ACS was considered to be triggered by erosions and plaque ruptures.

Among patients with previous ACS and who were receiving high-intensity statin therapy, the risk of recurrent ischemic cardiovascular events was lower among those who received alirocumab compared with that among those who received placebo [9]. Through this case, the importance of lipid management of FH patients was reconfirmed. There are several reports that PCSK9 antibodies have reduced cardiovascular events, but they have not been investigated in PCSK9 antibody discontinuation cases.

A limitation of this study was that the assessment of tissue characteristics inside the DES was only by grayscale IVUS. Second, in the case of FH patients, although the atorvastatin administration can be increased to 40 mg daily, the side effects of statins are reported to increase in a dose-dependent manner. Thus, we decided to gradually increase the dose to target LDL-C below 70 mg/dL. Therefore, it cannot be denied that discontinuation of the PCSK9 antibody was not directly associated with recurrence. Third, the patient and other family members were not genotyped.

In conclusion, we herein reported, to the best of our knowledge, the first case of ACS after discontinuation of the PCSK9 antibody in an FH patient.

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Disclosure of conflicts of interest

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jccase.2019.08.007.

References

[1] Bujo H, Takahashi K, Saito Y, Maruyama T, Yamashita S, Matsuzawa Y, et al. Clinical features of familial hypercholesterolemia in Japan in a database from 1996-1998 by the research committee of the ministry of health, labour and welfare of Japan. J Atheroscler Thromb 2004;11(3):146–51.
[2] Kastelein JJ, Ginsberg HN, Langslet G, Hovingh GK, Ceska R, Dufour R, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. Eur Heart J 2015;36(43):2996–3003.
[3] Raal FJ, Stein EA, Dufour R, Turner T, Civeira F, Burgess L, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet 2015;385(9965):331–40.
[4] Harada-Shiba M, Arai H, Ishigaki Y, Ishibashi S, Okamura T, Ogura M, et al. Guidelines for diagnosis and treatment of familial hypercholesterolemia 2017. J Atheroscler Thromb 2018;25(8):751–70.
[5] Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 2013;34(45). 3478-90a.
[6] Gidding SS, Champagne MA, de Ferranti SD, Defesche J, Ito MK, Knowles JW, et al. The agenda for familial hypercholesterolemia: a scientific statement from the american heart association. Circulation 2015;132(22):2167–92.
[7] Shirahama R, Ono T, Nagamatsu S, Sueta D, Takashio S, Chitose T, et al. Coronary artery plaque regression by a PCSK9 antibody and Rosuvastatin in double-heterozygous familial hypercholesterolemia with an LDL receptor mutation and a PCSK9 V4I mutation. Intern Med 2018;57(24):3551–7.
[8] Nakazawa G, Otsuka F, Nakano M, Vorpahl M, Yazdani SK, Ladich E, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. J Am Coll Cardiol 2011;57(11):1314–22.
[9] Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379(22):2097–107.