JACC: CASE REPORTS VOL. 2, NO. 12, 2020

MINI-FOCUS ISSUE: INTERVENTIONAL CARDIOLOGY

INTERMEDIATE

CASE REPORT: CLINICAL CASE

Refractory In-Stent Restenosis Attributable to Eruptive Calcified Nodule

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ABSTRACT

A 75-year-old female patient on hemodialysis presented with non-ST-segment elevation myocardial infarction. After successful primary percutaneous coronary intervention, in-stent restenosis (ISR) occurred 3 consecutive times. Intravascular imaging assessment during the repeated percutaneous coronary intervention indicated that the ISR was not associated with neointimal hyperplasia but was mainly attributed to a calcified nodule, which protruded into the lumen. We applied excimer laser catheter ablation to avoid another ISR. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2020;2:1872–8) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 75-year-old woman was hospitalized because of prolonged centralized chest pain without any palpitation and shortness of breath. There was no remarkable physical examination including cardiac murmur and respiratory sounds. Her blood pressure and heart rate were 139/63 mm Hg and 58 beats/min, respectively.

LEARNING OBJECTIVES

- Following primary PCI for CN, refractory ISR occurred, and its mechanism was likely a repeated protrusion of CN rather than neointimal hyperplasia.
- A distinct mechanism of ISR at the CN underscores the need for another therapeutic approach to optimize its PCI outcome.
- It is important to consider the use of debulking devices for modifying the CN before stent implantation.

PAST MEDICAL HISTORY

From her previous medical background, she required maintenance hemodialysis because of diabetic nephropathy. We suspected immediately acute coronary syndrome (ACS).

INVESTIGATIONS

Electrocardiography demonstrated ST-segment depression at inferior leads. Echocardiography showed hypokinesis of inferior wall motion. Furthermore, troponin T level was 0.653 ng/ml. Her estimated glomerular filtration rate, hemoglobin, and platelet count were 3.8 ml/min/1.73 m^2, 12.5 g/dl, and 184,000/μl, respectively. Emergent coronary angiography identified severe stenosis with calcification at the middle segment of right coronary artery (RCA)

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

Manuscript received June 17, 2020; accepted June 22, 2020.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2020.06.035

(Video 1), whereas there was no significant stenosis in the left coronary artery. Following coronary angiography, primary percutaneous coronary intervention (PCI) was performed.

MANAGEMENT

Intravascular ultrasound (IVUS) was used to evaluate the culprit lesion before PCI. It visualized the protruding shape of multiple calcification plates suggestive of a calcified nodule (CN) (**Figure 1D**, Video 2). After balloon angioplasty, one 3.5 mm × 18 mm biolimus-eluting stent (Nobori, Terumo, Tokyo, Japan) was implanted, which enabled to compress protruding calcium plates with minimum stent area at 8.64 mm^2 (**Figure 1E**, Video 3). She was discharged following the commencement of 100-mg aspirin and 75-mg clopidogrel.

Eight months later, she presented our emergency room again because of the recurrence of chest pain under the aforementioned dual antiplatelet therapy (DAPT). Troponin T level was 0.224 ng/ml. A hypokinetic inferior wall was observed by echocardiography. Coronary angiography revealed in-stent restenosis (ISR) within the previously implanted drug-eluting stent (DES) (**Figure 2A**). IVUS showed the reprotrusion of calcification plates into the lumen. On optical coherence tomography (OCT) imaging, in addition to neointimal hyperplasia, multiple high-intensity signals with its substantial attenuation existed and caused lumen narrowing at the ISR site. These findings indicated that ISR was attributable to mainly eruptive CN (**Figure 2D**, Supplemental

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CN = calcified nodule

DAPT = dual-antiplatelet therapy

DES = drug-eluting stent

ELCA = excimer laser catheter ablation

ISR = in-stent restenosis

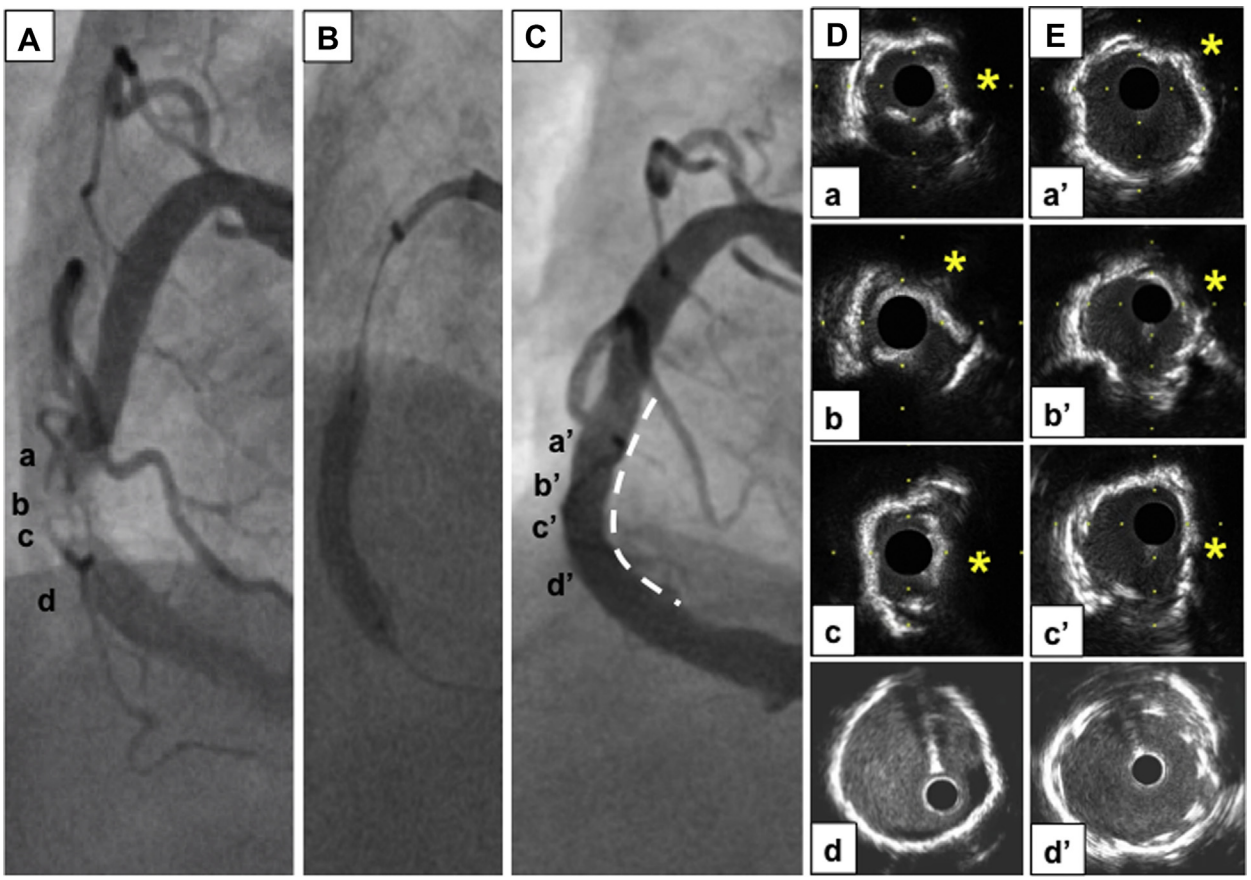
IVUS = intravascular ultrasound

PCI = percutaneous coronary intervention

OCT = optical coherence tomography

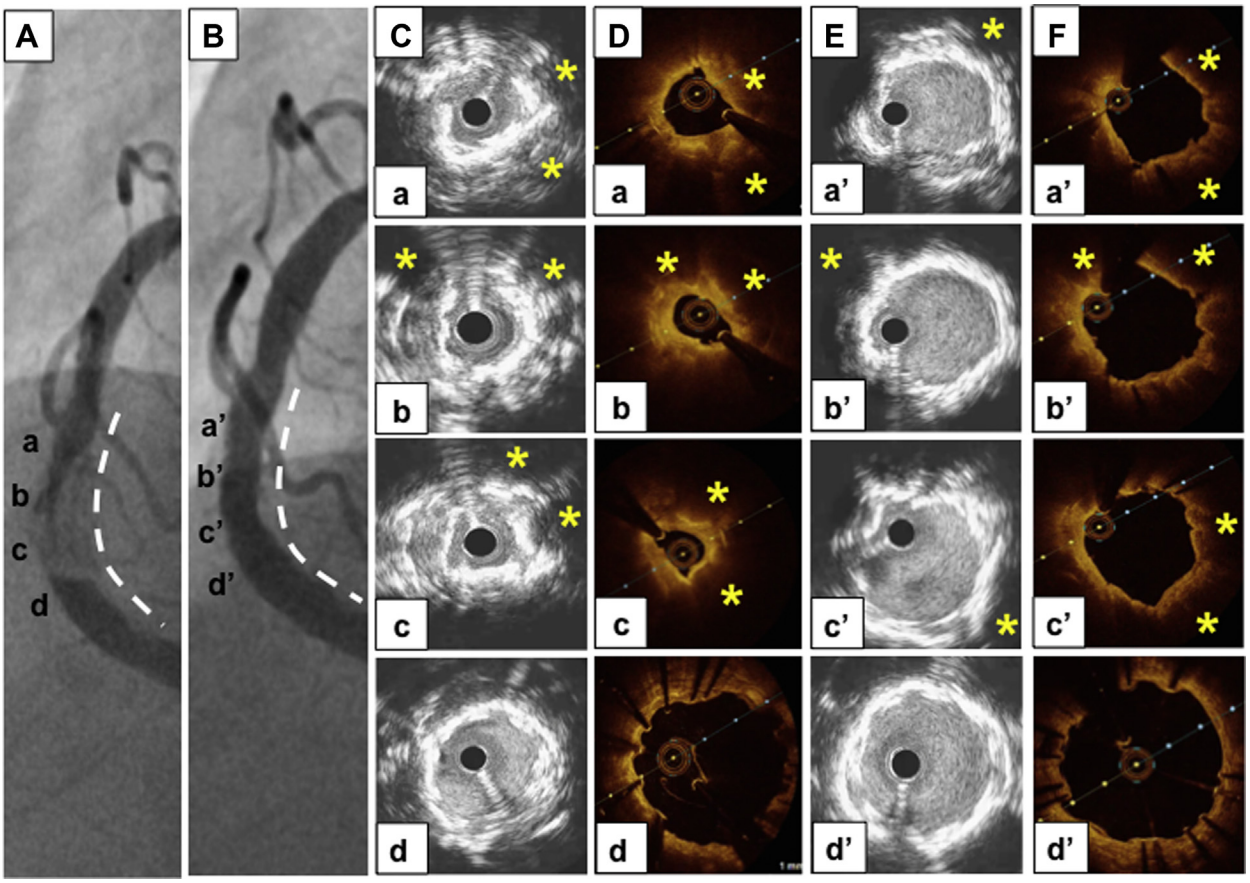
RCA = right coronary artery

FIGURE 1 Primary PCI for Calcified Nodule



(A) Coronary angiography prior to percutaneous coronary intervention. **(B, C)** The first percutaneous coronary intervention. The **white dotted line** indicates the segment that received the implantation of biolimus-eluting stent. **(D)** Baseline intravascular ultrasound (IVUS) images. Protruding calcification with its irregular surface **(asterisk)** was observed on IVUS imaging **(a to c)**. These morphological features indicated calcified nodule. **(E)** Final IVUS images. Protruding calcification plates **(asterisk)** were compressed by stent struts **(a' to c')**.

FIGURE 2 First In-Stent Restenosis 8 Months After Primary PCI



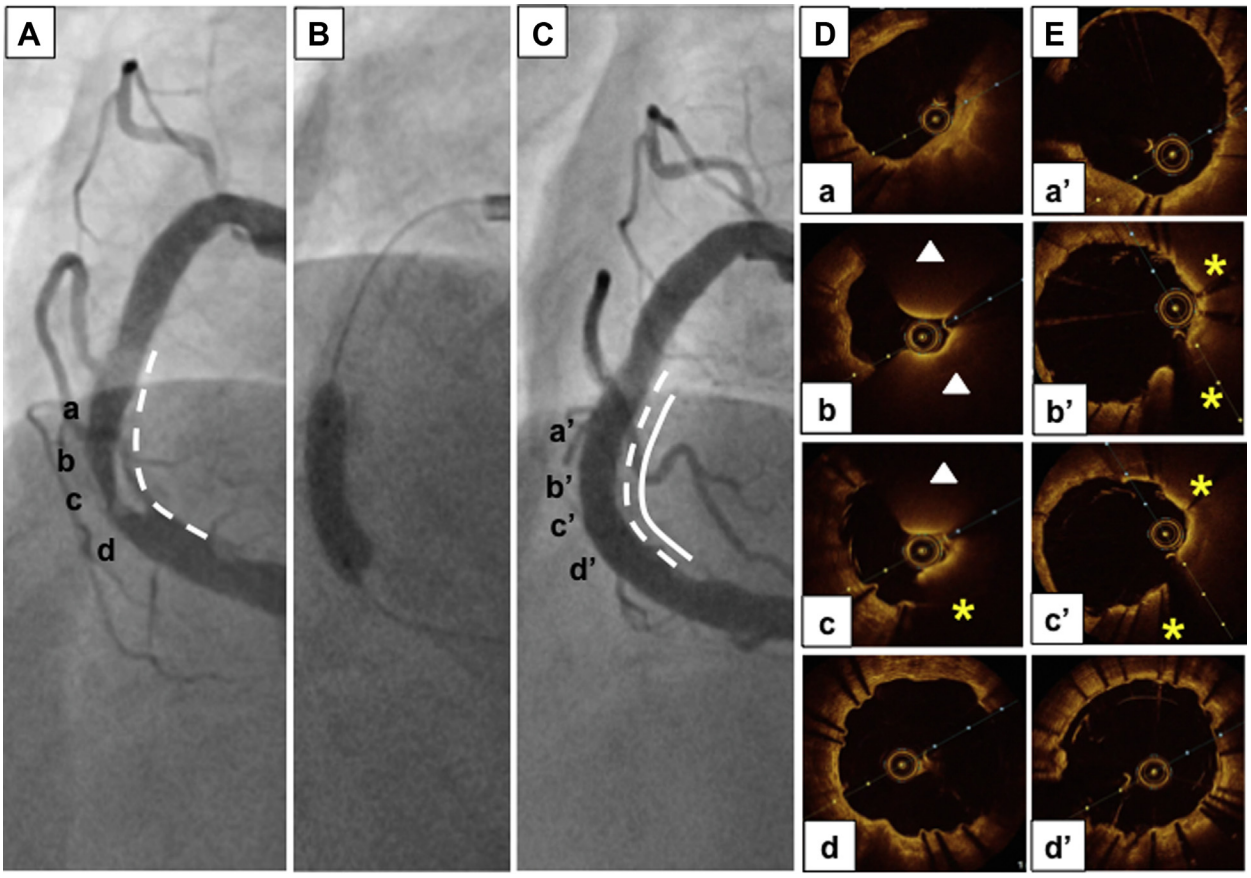
(A) Coronary angiography 8 months after the first percutaneous coronary intervention. In-stent restenosis within the previously implanted drug-eluting stent **(white dotted line)** was observed. **(B)** Coronary angiography after the use of drug-coating balloon. **(C, D)** Pre–intravascular ultrasound and optical coherence tomography images. Multiple calcification plates **(asterisk)** were protruding again through the stent struts **(a to c)**. **(d)** There is no calcified nodule. **a' to d'** corresponds to **a to d** in **A and D**. **(E, F)** Final intravascular ultrasound and optical coherence tomography images. Protruding calcification plates **(asterisk)** were compressed.

Figures 1 and 2, Video 4). Culprit lesion was treated by a 4.0-mm drug-coating balloon (SeQuent Please, B. Braun Berlin, Germany) (**Figure 2F**, Video 5). Given that $P2Y_{12}$ reaction units measured by VerifyNow (Instrumentation Laboratory, Bedford, Massachusetts) were 295 under 75-mg clopidogrel use, it was switched to 3.75-mg prasugrel.

She required the third urgent hospitalization because of non-ST-segment elevation ACS 3 months after the second PCI. This recurrence of ACS was because of the second ISR in the RCA confirmed by coronary angiography. OCT prior to PCI demonstrated protruding mass characterized by high signal intensity with remarkable attenuation, suggesting the presence of a CN (**Figure 3D**, Supplemental Figure 3, Video 6). Of note, there was red thrombus attaching to the CN despite continuing same DAPT regimen. A 4.0 mm × 15 mm additional everolimus-eluting stent (Xience, Abbott Vascular, Santa Clara, California) was implanted to cover the protruding mass and thrombus (**Figure 3E**, Video 7).

She was rehospitalized because of non-ST-segment elevation ACS 6 months after the third PCI, although she was taking DAPT. Again, OCT imaging elucidated neointimal hyperplasia as well as protruding high-intensity mass with remarkable attenuation (**Figure 4E**, Supplemental Figure 4, Video 8). Debulking with excimer laser catheter ablation (ELCA) (1.7-mm Vitesse-Cos RX catheter, Spectranetics, Colorado Springs, Colorado) was performed with an incremental energy setting at 40 mJ/60 Hz. OCT imaging after ELCA revealed the effective ablation of the CN (**Figure 4G**, Video 9). Procedural-related minor coronary perforation was resolved by 3.5-mm

FIGURE 3 Second In-Stent Restenosis 3 Months After the Second PCI



(A) Coronary angiography 3 months after the second percutaneous coronary intervention. **(B, C)** The third percutaneous coronary intervention. Additional drug-eluting stent **(white solid line)** was implanted within the previous stent **(white dotted line)**. **(D)** Baseline optical coherence tomography images. **(E)** Final optical coherence tomography images. **Asterisks and white triangles** indicate the calcified nodule and red thrombus, respectively. **a to d** indicate the site imaged by OCT in **B**. **a' to d'** correspond to **a to d** in **A**.

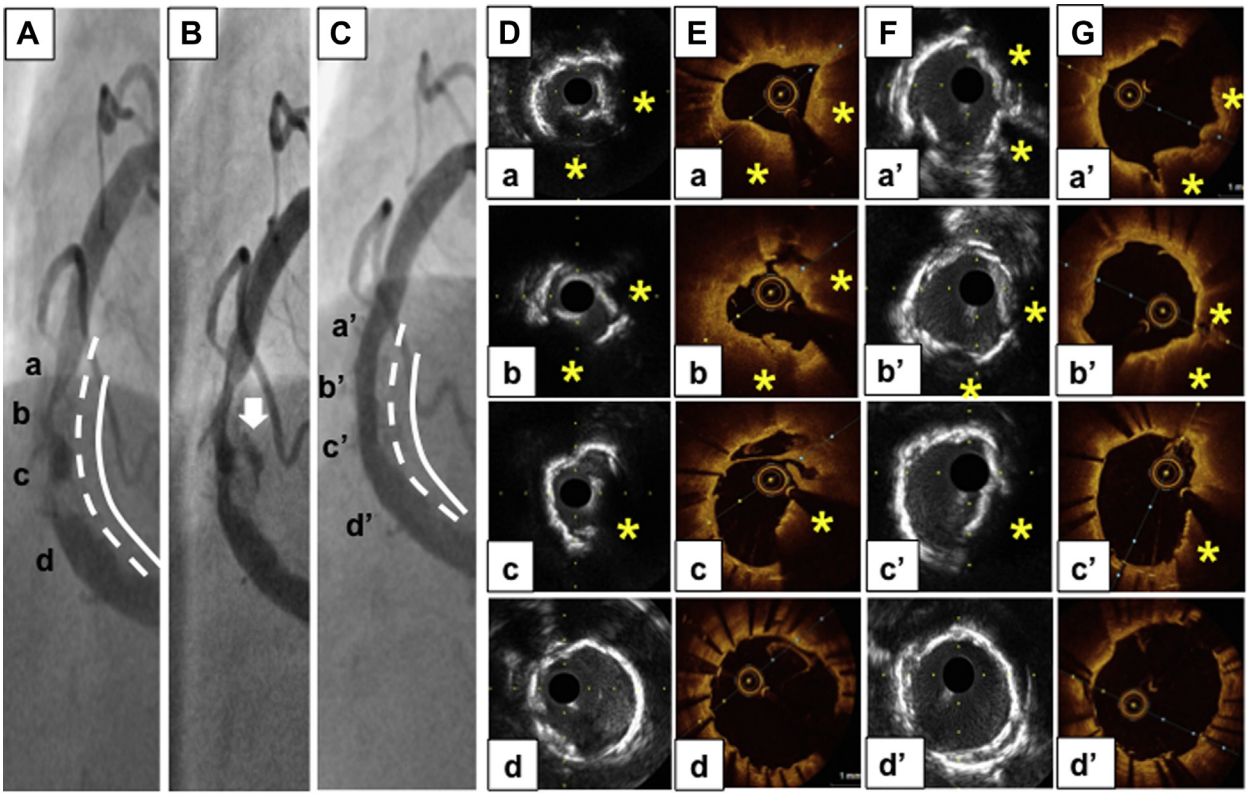
perfusion balloon (Ryusei, KANEKA Medics, Osaka, Japan) (**Figure 4B**, Video 10). A 3.5-mm drug-coating balloon (SeQuent Please, B. Braun, Berlin, Germany) was used to optimize this PCI procedure.

DISCUSSION

This case provides mechanistic insights into the refractory ISR at the CN (1–6). In this case, the implantation of a biolimus-eluting stent enabled the acquisition of optimal stent expansion. However, ISR occurred and it was presumably driven by the protrusion of the CN, rather than neointimal hyperplasia. Moreover, this dynamic response of the CN after favorable dilatation was repeatedly observed at every ISR. Recent pathohistological study reported 2 different mechanisms of ISR at the CN, which included: 1) protrusion of the CN through the stent struts; or 2) calcification of thrombus or neointima within the implanted stent (7). The protruding mass characterized by high signal intensity with remarkable attenuation on OCT was identified at the culprit lesion under DAPT. Therefore, the former mechanism seems more likely to be responsible for the refractory ISR in our case.

Every ISR occurred between 3 and 8 months after PCI and presented as ACS. Because ISR is generally observed around 8 months following PCI, the timing of every ISR in this case was quite earlier compared with findings from clinical trials. CN has been reported to be more frequently located at the middle segment of RCA, which receives much mechanical stress because of coronary hinge motion through beating (8). Moreover, stent implantation at this segment may make it more rigid. As such, more susceptible nature of coronary

FIGURE 4 Third In-Stent Restenosis 6 Months After the Third PCI



(A) Coronary angiography 6 months after the third percutaneous coronary intervention. The **white dotted line** indicates the implanted biolimus-eluting stent, and the **white solid line** indicates the implanted everolimus-eluting stent. **(B, C)** The fourth percutaneous coronary intervention with excimer laser coronary angioplasty. **(B)** Following excimer laser coronary angioplasty use, minor perforation occurred **(white arrow)**. **(D, E)** Pre-intravascular ultrasound and optical coherence tomography images. **(F, G)** Final intravascular ultrasound and optical coherence tomography images. **Asterisks** indicate the calcified nodule. **a to d** indicates the site imaged by IVUS and OCT in **D and E**. **a' to d'** corresponds to **a to d** in **A**.

segment to stress as well as its stent-induced greater rigidity may be a potential substrate for causing much stress, thereby resulting in the rapid and repeated eruption of the CN.

The current case indicates a potential benefit of the debulking procedure for CN. Currently, there is no evidence about its efficacy and difference in each debulking device. In our case, target lesion revascularization was not needed for 2 years after ELCA use. Orbital atherectomy is a recently developed coronary atherectomy device. It enables the modulation of calcification by both its advancement and pullback via wire bias. This feature may effectively modify the CN with its eccentric structure. Further investigation is warranted to elucidate a lesion-modification strategy with orbital atherectomy, ELCA, and other devices for CN.

In this case, coronary artery bypass surgery was an alternative option for revascularization. Because any significant stenosis was not identified in the left coronary artery throughout her clinical course, we selected PCI for repeated ISR.

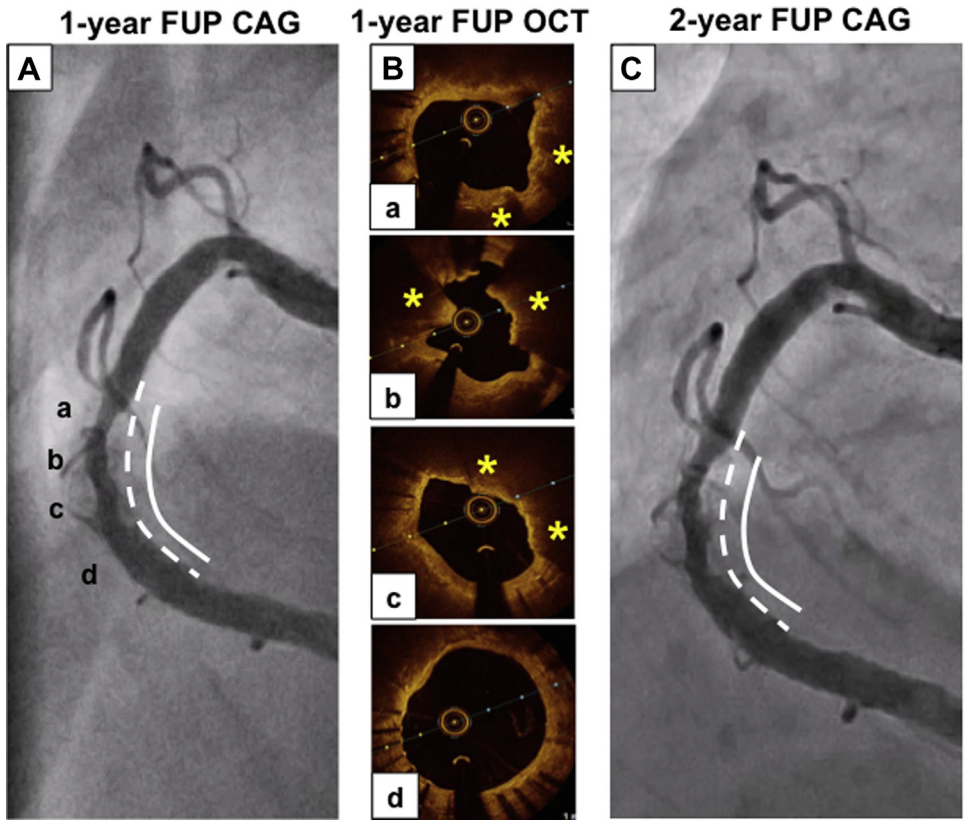
FOLLOW-UP

Follow-up coronary angiography 12 months after the last PCI showed a fourth restenosis at the CN lesion. However, PCI was deferred because of its fractional flow reserve at 0.86 (Figures 5A and 5B). OCT imaging visualized the presence of multiple protruding CNs, but the lumen area was not substantially compromised. The repeated coronary angiography 2 years after the last PCI identified that the degree of stenosis at the ISR lesion did not change (Figure 5C). She continued to take DAPT after the last PCI.

CONCLUSIONS

In the current case, the CN exhibited refractory ISR following newer-generation DES implantation.

FIGURE 5 Follow-Up Coronary Angiography



(A) One-year follow-up (FUP) coronary angiography (CAG) after the fourth percutaneous coronary intervention. **(B)** Optical coherence tomography (OCT) images 1 year after the fourth PCI. **(C)** Two-year FUP CAG after the fourth PCI. The **white dotted line** indicates the implanted biolimus-eluting stent, and the **white solid line** indicates the implanted everolimus-eluting stent. **a to d** indicate the site imaged by OCT in **B**.

Intravascular imaging elucidated a distinct mechanism of ISR, which is presumably derived by repeated protrusion of a CN. These findings highlight CN as a high-risk plaque phenotype which requires repeat revascularization. Considering that debulking with ELCA effectively modulated the CN and the recurrence of ISR did not occur after the procedure, this strategy may be a potential first-line approach to treat the CN prior to stent implantation. Future studies are warranted to evaluate the efficacy of debulking devices including ELCA, rotablator, orbital atherectomy, and lithotripsy on CN.

AUTHOR RELATIONSHIP WITH INDUSTRY

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS calcified nodule, in-stent restenosis, intravascular imaging, percutaneous coronary intervention

APPENDIX For supplemental videos and figures, please see the online version of this paper.