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

EDITORIAL COMMENT

Recognition of Recurrent Stent Failure Due to Calcified Nodule

Between a Rock and a Hard Place*

Jeffrey W. Moses, MD,[a,b,c] Eisuke Usui, MD,[a,b] Akiko Maehara, MD[a,b]

Calcified nodule (CN) is known as the least frequent (~5%) morphology causing thrombotic acute coronary syndrome. CN is an accumulation of small calcium fragments accompanying fibrin or platelet-rich thrombi, presumably a disruption of a fibrous cap due to a fracture of an underlying calcified plate (1). The prevalence of CN has been reported as 16% per vessel and 30% per patient in the nonculprit lesions using 3-vessel intravascular ultrasound (IVUS) (2) and 4.2% of culprit lesions using optical coherence tomography (OCT). Maximum calcium angle, coronary artery hinge motion, and hemodialysis are associated with the presence of CN (3). Morofuji et al. (4) reported that half of the heavily calcified lesions requiring rotational atherectomy had CN and that CN was associated with the worse 5-year adverse events, suggesting a mechanism of stent failure by CN that may not be resolved simply by adequate stent expansion.

Mori et al. (5) reported 2 different types of CN-related in-stent thrombosis in autopsy cases: 1) CN within the neointima (neoatherosclerosis) causing a thrombotic occlusion; and 2) CN without neointimal hyperplasia, suggesting early luminal thrombosis due to a reprotrusion of the CN through the stent. The first one is a similar mechanism of thrombosis to de novo CN, while the second one seems to be a unique phenomenon related to the CN in the stent (5).

In this issue of *JACC: Case Reports*, Nakano et al. (6) described a challenging case of a 75-year-old woman on hemodialysis who presented non-ST-segment elevation myocardial infarction and CN in the culprit lesion was treated with a drug-eluting stent. This patient presented at 8, 11, and 17 months with repeated non-ST-segment elevation myocardial infarction each time due to reprotrusion of the CN into the lumen without significant neointimal hyperplasia as determined by OCT or IVUS. Finally, after laser atherectomy, the culprit lesion remains nonobstructive, though follow-up OCT still demonstrated a non-flow-limiting reprotruding CN. Mechanism of this case seems to be the second type of CN-related thrombotic event described by Mori et al. (5).

Table 1 summarizes 6 cases reports (current and 5 others) describing recurrent in-stent restenosis (ISR) of which mechanism was confirmed as reprotruding CN by OCT or IVUS without significant neointimal hyperplasia at the CN site (i.e., those CNs were not a part of neoatherosclerosic process, but rather reprotrusion of original de novo CN through the stent) (7–11). Clinical and lesion characteristics include: 1) 4 patients on hemodialysis due to diabetic nephropathy; 2) myocardial infarction presentation in 4 patients at the time of ISR; 3) time to event being relatively early compared with regular ISR (median of 5.5 months from index procedure); 4) recurrent ISRs in 3 patients; 5) 3 cases being in proximal to mid right coronary artery and 1 case being at the hinge motion of saphenous vein graft; and 6) 2 cases with stent fractures at the site of CN. In summary, de novo CN appears at the hinge motion of severely calcified coronary artery, and the stented CN still has

*Editorials published in *JACC: Case Reports* reflect the views of the authors and do not necessarily represent the views of *JACC: Case Reports* or the American College of Cardiology.

From [a]Cardiology, NewYork-Presbyterian Hospital/Columbia University Medical Center, New York, New York; [b]Clinical Trials Center, Cardiovascular Research Foundation, New York, New York; and [c]Cardiology, St. Francis Hospital, Roslyn, New York.

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.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2020.09.004

TABLE 1 Case Reports Describing Recurrent Events After Stenting on CN

First Author (Ref. #)	Patient Presentation, Imaging Findings, Treatment, and Outcome
Current report (6)	CN in the mid RCA caused NSTEMI and treated with stent. At 8, 11, and 17 months, the patient experienced 3 NSTEMIs due to reprotruding CN in the stent. Treatments includes drug-coating balloon at first ISR, new stent at second ISR, and laser at third ISR. In the subsequent 2 yrs, patient did not have clinical event, though follow-up OCT showed non-flow-limiting reprotruding CN.
Yumoto et al. (7)	CN in the proximal RCA caused stable angina and treated with scoring balloon and stent. At 5 months, the patient experienced STEMI due to reprotruding CN in the stent.
Kawai et al. (8)	CN in the mid left circumflex artery caused NSTEMI and was treated with stent. At 4 and 9 months, the patient experienced 2 NSTEMIs due to reprotruding CN in the stent. Treatments includes scoring balloon and stent at first ISR and coronary bypass at second ISR because of multivessel disease.
Kaihara et al. (9)	CN in the mid left anterior descending artery caused unstable angina and treated with scoring balloon and stent. At 9 months, patient experienced stable angina due to reprotruding CN and neointimal hyperplasia in the stent, which was treated by cutting balloon.
McCutcheon et al. (10)	A proximal RCA lesion was treated by stent. At 6 months and 2 yrs, the patient experienced ISR, and OCT diagnosed protruding CN in the stent at 2 yrs. Eight years later, patient presented with unstable angina due to reprotruding CN through the fractured stent. Following lithotripsy, additional stents were implanted.
Uemura et al. (11)	CN in a 36-year-old saphenous vein graft caused stable angina and was treated with stent. At 3 months, 2 weeks after cessation of $P2Y_{12}$ inhibitor, the patient experienced STEMI due to reprotruding CN through stent fracture.

CN = calcified nodule; ISR = in-stent restenosis; NSTEMI = non-ST-segment elevation myocardial infarction; OCT = optical coherence tomography; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction.

mechanical stresses, resulting in reprotrusion of CN with or without visible stent fracture and frequently causes recurrent thrombotic events. Because of incomplete noncompliant balloon expansion, scoring or cutting balloon was used in 3 cases, lithotripsy was used in 1 case, and the current case was treated by laser atherectomy. Considering the mechanism of ISR (reprotrusion of CN) and a high prevalence of stent fracture, debulking of CN without a stent at the first time could be considered (12). However, because CN is protruding into the lumen and its eccentric shape, a caution must be taken to avoid perforation due to a wire bias to the normal site, which was observed in the current case.

One can speculate as to the mechanism of action of the laser: as excimer laser ablates only on contact, one wonders whether the acoustic effects of laser energy-fractured calcific segments that allowed more successful balloon compression and less reprotrusion. The authors do appropriately cite orbital atherectomy and intravascular lithotripsy as potential alternatives as well.

In summary, this case highlights an infrequent but vexing problem in percutaneous coronary intervention treatment of acute coronary syndromes and demonstrates the value of novel case reports in stimulating new approaches to rare problems.

AUTHOR RELATIONSHIP WITH INDUSTRY

Dr. Maehara has received institutional grant support from and served as a consultant for Abbott Vascular and Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Jeffrey W. Moses, Columbia University Medical Center, 161 Fort Washington Avenue, New York, New York 10032. E-mail: jm2456@cumc.columbia.edu.

REFERENCES

1. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death. Arterioscler Thromb Vasc Biol 2000;20:1262–75.

2. Xu Y, Mintz GS, Tam A, et al. Prevalence, distribution, predictors, and outcomes of patients with calcified nodules in native coronary arteries: a 3-vessel intravascular ultrasound analysis from providing regional observations to study predictors of events in the coronary tree (PROSPECT). Circulation 2012;126:537–45.

3. Lee T, Mintz GS, Matsumura M, et al. Prevalence, predictors, and clinical presentation of a calcified nodule as assessed by optical coherence tomography. J Am Coll Cardiol Img 2017;10:883–91.

4. Morofuji T, Kuramitsu S, Shinozaki T, et al. Clinical impact of calcified nodule in patients with heavily calcified lesions requiring rotational atherectomy. Catheter Cardiovasc Interv 2020 Apr 7 [E-pub ahead of print].

5. Mori H, Finn AV, Atkinson JB, Lutter C, Narula J, Virmani R. Calcified nodule: an early and late cause of in-stent failure. J Am Coll Cardiol Intv 2016;9:e125–6.

6. Nakano H, Kataoka Y, Otsuka F, et al. Refractory in-stent restenosis attributable to eruptive calcified nodule. J Am Coll Cardiol Case Rep 2020;2:1872–8.

7. Yumoto K, Kanaya T, Tanaka S, Fukuzawa T, Watanabe T, Aoki H. Calcified nodule as an unsolved cause of coronary stent thrombosis in the new-generation drug-eluting stent era. Cardiovasc Interv Ther 2018;33:169–70.

8. Kawai K, Akahori H, Imanaka T, et al. Coronary restenosis of in-stent protruding bump with rapid progression: optical frequency domain imaging and angioscopic observation. J Cardiol Cases 2019;19:12–4.

9. Kaihara T, Higuma T, Kotoku N, et al. Calcified nodule protruding into the lumen through stent

struts: an in-vivo OCT analysis. Cardiovasc Revasc Med 2020 Mar 11 [E-pub ahead of print].

10. McCutcheon K, Bennett J, Adriaenssens T. Double stent fracture and in-stent restenosis due to nodular calcification treated with Shockwave coronary intravascular lithotripsy. Catheter Cardiovasc Interv 2020 Jan 16 [E-pub ahead of print].

11. Uemura Y, Tanaka A, Takemoto K, et al. Late stent thrombosis concurrent with stent fracture at calcified nodule lesion in saphenous vein graft. J Am Coll Cardiol Intv 2019;12:e199–200.

12. Matsuda Y, Ashikaga T, Sasaoka T, et al. Ostial left circumflex lesion with calcified nodule successfully treated with excimer laser coronary atherectomy and drug-coated balloon. J Cardiol Cases 2020;22:32–5.

KEY WORDS acute coronary syndrome, atherosclerosis, percutaneous coronary intervention, stents