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Case Report

Very Early Progression of an In-Stent Calcified Nodule 2 Weeks After Drug-Eluting Stent Implantation in the Calcified Lesion

Naoko Higashino, MD, Takayuki Ishihara, MD, Osamu Iida, MD, Takuya Tsujimura, MD, Yosuke Hata, MD, Taku Toyoshima, MD, Sho Nakao, MD, and Toshiaki Mano, MD, PhD

Kansai Rosai Hospital Cardiovascular Center, Amagasaki, Japan

ABSTRACT

In-stent calcified nodules (CNs) are one of the mechanisms of in-stent restenosis, but their underlying cause has not been elucidated. We report a case of a patient with early stent thrombosis due to an in-stent CN only 2 weeks after drug-eluting stent implantation. The fact that the in-stent CN was detected only 2 weeks after the initial percutaneous coronary intervention means that the underlying mechanism was the progression of the CN, indicating that in-stent CNs can occur even in the subacute phase. After percutaneous coronary intervention for a severe calcified lesion, very early progression of CNs can occur, and they require close follow-up and intensive antiplatelet therapy.

RÉSUMÉ

La présence d'un nodule calcifié (NC) est l'un des facteurs pouvant donner lieu à une resténose intra-endoprothèse, mais la cause sous-jacente n'est pas encore bien comprise. Nous décrivons ici le cas d'une patiente qui a subi une thrombose précoce due à un NC à l'intérieur de la prothèse à peine deux semaines après la mise en place d'une endoprothèse médicamentée. La détection du NC dans la prothèse seulement deux semaines après l'intervention percutanée initiale signifie que la progression du NC constitue la cause sous-jacente et indique que des NC peuvent survenir même au cours de la phase subaiguë. Après une intervention coronarienne percutanée pour traiter une lésion calcifiée grave, une progression très précoce des NC peut avoir lieu, d'où l'importance d'un suivi rigoureux et d'un traitement antiplaquettaire intensif.

An 82-year-old Japanese woman suffered from effort angina pectoris due to severe stenosis with severe calcification in the left anterior descending artery (Fig. 1A, parts a and b). She had coronary risk factors—hypertension, diabetes mellitus, and dyslipidemia. She also had undergone hemodialysis for chronic kidney disease due to diabetic nephropathy, and endovascular therapy for peripheral artery disease. Percutaneous coronary intervention (PCI) was performed with a rotational atherectomy with a 1.5-mm burr and orbital atherectomy, followed by the implantation of 2 durable-polymer everolimus-eluting stents (Xience Skypoint 2.5 mm × 18 mm, and 3.25 mm × 38 mm, Abbott Vascular, Santa Clara, CA), which resulted in sufficient angiographic results (Fig. 1A, part c). However, intravascular ultrasound images showed underexpansion and moderate protrusion of calcification at the end of the procedure (Fig. 1A, part d; Video 1, view video online). Dual-antiplatelet therapy with aspirin and clopidogrel was started before the PCI and was continued subsequent to the PCI. However, 2 weeks after the PCI, the patient suddenly experienced chest pain at rest. Electrocardiography showed ST-segment depression in the V3-V6 leads. Transthoracic echocardiography revealed a reduced ejection fraction and hypokinesis of the anterior left ventricular wall. Emergent coronary angiography demonstrated severe stenosis in the stented segment (Fig. 1B, part a). We diagnosed this event as early stent thrombosis. Another PCI was subsequently attempted, and intravascular imaging analyses with intravascular ultrasound (Fig. 1B, part b; Video 2, view video online) and optical coherence tomography (Fig. 1B, part c; Video 3, view video online) after the thrombus aspiration showed in-stent calcified nodules (CNs). We suspected that the CNs were the cause of early stent thrombosis, and we thought that an atherectomy of the CNs was necessary. We performed a rotational atherectomy with a larger (2-mm) burr (Videos 4 and 5, view videos online), followed by 2.5-mm drug-coated balloon inflation, which resulted in adequate expansion (Fig. 1B, parts d and e; Videos 6 and 7, view videos online). The chest pain was clearly improved post-PCI. The pathology findings on the

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Corresponding author: Dr Takayuki Ishihara, Kansai Rosai Hospital Cardiovascular Center, 3-1-69 Amagasaki, Hyogo 660-8511, Japan. Tel.: +81-6-6416-1221; fax: +81-6-6419-1870.

E-mail: t.ishihara31@gmail.com

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Novel Teaching Points

- In-stent CNs are one of the mechanisms of in-stent restenosis. The mechanism underlying their formation has not been elucidated.
- It was reported that protrusion of a CN, followed by a calcifying fibrin thrombus, could cause early (2-3 months) in-stent CNs.
- Judging from the current case in which early stent thrombosis due to an in-stent CN was detected only 2 weeks after drug-eluting stent implantation, one of the mechanisms leading to an in-stent CN is the progression of one or multiple underlying CNs.

aspirated material indicated small, fragmented nodules of calcification surrounded by fibrin and erythrocytes, which is consistent with in-stent CNs (Fig. 2).

Discussion

A CN is defined as a lesion with fibrous cap disruption and thrombi associated with eruptive, dense, calcific nodules.[1] In terms of the mechanism of the organization of CNs, Torii et al. mentioned that the necrotic core calcium fragments into multiple pieces, causing capillary breaks and intraplaque hemorrhage, increasing plaque volume that eventually protrudes into the lumen, disrupting the fibrous cap and overlying endothelium, forming CNs or nodular calcification areas.[2] A recent clinical study demonstrated that CNs were observed in 13% of the cases with definite second-generation drug-eluting stent thrombosis.[3] In addition, CNs have been reported to have a poor prognosis, even after treatment, and around 78% of in-stent restenosis at CN lesions was caused by the formation of a protruding mass with acoustic shadowing rather than neointimal hyperplasia, indicating that intrusion of the CN was the cause of in-stent restenosis after stenting of the CN.[4] Also, in-stent CNs are one of the mechanisms of in-stent restenosis and were reported to be particularly common in dialysis patients[5]; however, the mechanism has not been elucidated. Nakamura et al. noted that the protrusion of a CN followed by a calcifying fibrin thrombus might cause an early (2-3 months) in-stent CN.[5] In the present patient, the fact that the in-stent CNs were detected only 2 weeks after the initial PCI indicates that the underlying mechanism is as follows: the underlying CNs (the necrotic core calcium fragments) were manifested as a protrusion due to the debulking by the atherectomy devices and mechanical injury by balloon dilatation and stent implantation, and it progressed in the subacute phase. The current case indicates that acute coronary syndrome due to the

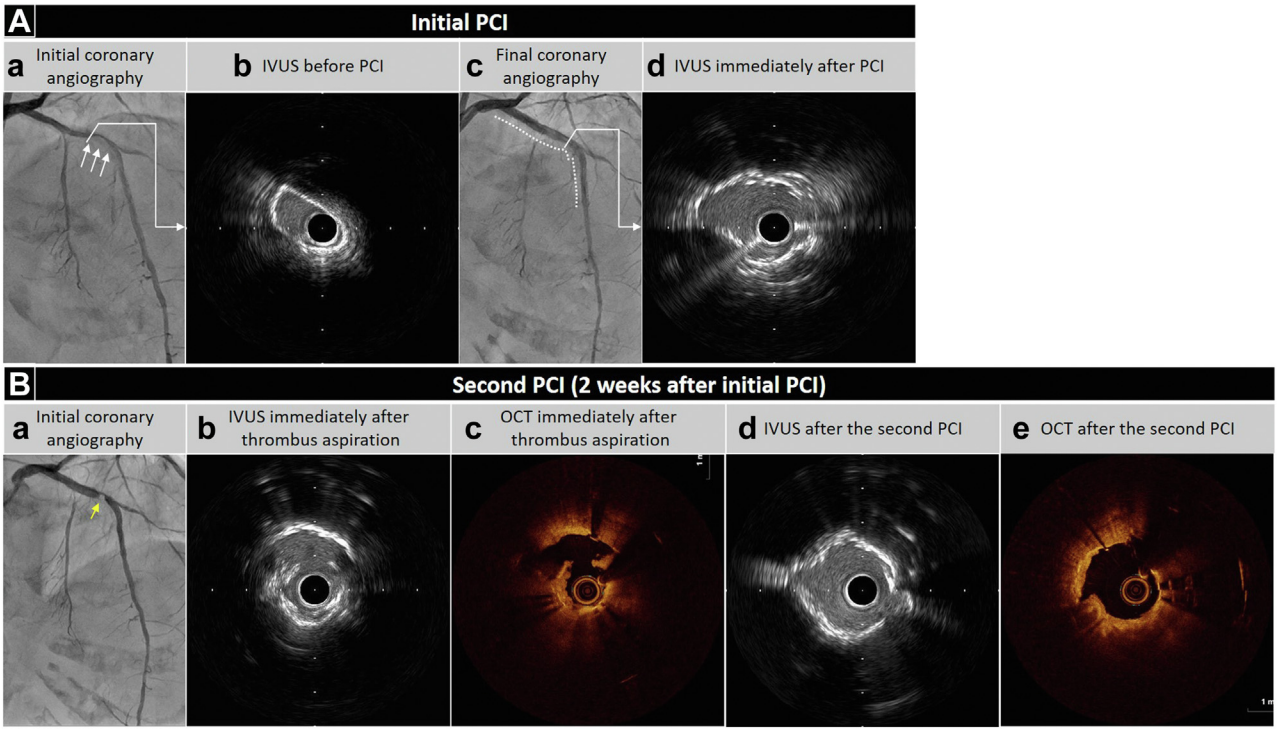

Figure 1. Coronary angiography, intravascular ultrasound (IVUS), and optical coherence tomography (OCT) of the initial and second percutaneous coronary intervention (PCI) (**A**) Initial PCI. (**a-c**) Sufficient angiographic results were obtained with the implantation of 2 drug-eluting stents (**white dashed lines**) for the severe calcified lesion in the left anterior descending artery (**white arrows**). (**d**) IVUS shows underexpansion and moderate protrusion of calcification at the end of the procedure. (**B**) Second PCI. (**a**) Coronary angiography shows severe stenosis in the stented segment (**yellow arrow**). (**b, c**) IVUS and OCT demonstrate the in-stent calcified nodules. (**d, e**) IVUS and OCT show adequate expansion after the prodecure.

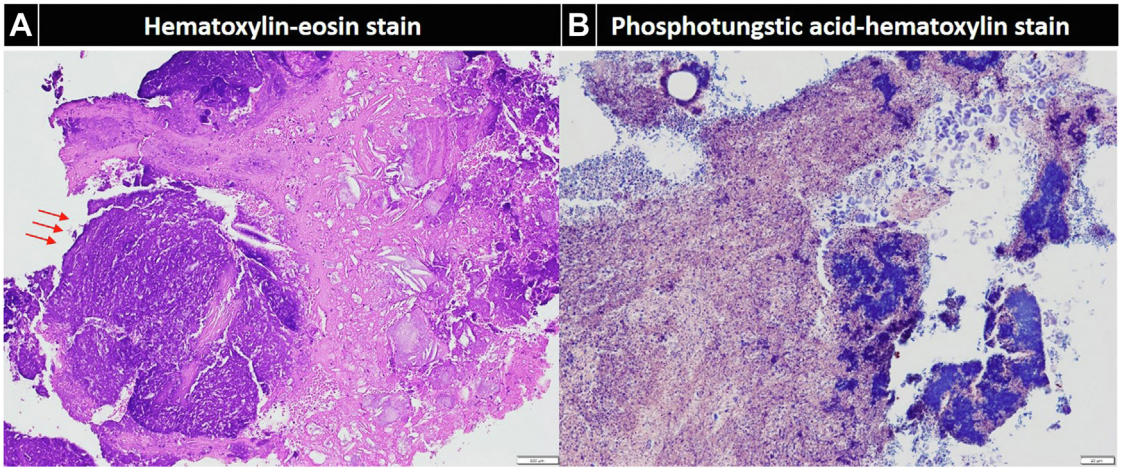

Figure 2. Histopathology of aspirated material. (**A**) Hematoxylin-eosin stain. (**B**) Phosphotungstic acid-hematoxylin stain. Small, fragmented nodules of calcification surrounded by fibrin and erythrocytes were detected (**red arrows**). Cholesterol crystal was also detected.

progression of in-stent CNs can occur even in the subacute phase (only 2 weeks after the initial PCI). After a PCI for calcified lesions, close follow-up and intensive antiplatelet therapy may be necessary. In addition, the fact that the index stent was under-expanded due to persistent calcification, which then became a nidus for early stent thrombosis, highlights the importance of adequate lesion preparation prior to stenting in PCI for calcified lesions.

Conclusions

We treated a patient with early stent thrombosis due to in-stent CNs that were present only 2 weeks after the implantation of a drug-eluting stent. This case suggests that (i) in-stent CNs can occur even in the subacute phase, and (ii) the underlying mechanism can be the progression of one or multiple underlying CNs.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2022.07.001.