Journal of Cardiology Cases 20 (2019) 84–87

Contents lists available at ScienceDirect

Journal of Cardiology Cases

journal homepage: www.elsevier.com/locate/jccase

Case Report

Failure of drug-coated balloon angioplasty to treat bare metal in-stent restenosis accompanied by late stent thrombosis but successful treatment of binary in-stent restenosis

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ARTICLE INFO

Article history:
Received 28 January 2019
Received in revised form 27 March 2019
Accepted 22 April 2019

Keywords:
Drug-coated balloon
Late stent thrombosis
Binary in-stent restenosis
Bare-metal stent
Excessive neointimal proliferation

ABSTRACT

Drug-coated balloons (DCB) are effective in treating in-stent restenosis (ISR) with neointimal proliferation after bare-metal stent (BMS) implantation, but it is unclear whether DCB are effective in treating BMS-ISR accompanied by thrombosis. An 84-year-old man with previous inferior myocardial infarction and atrial fibrillation developed acute myocardial infarction (AMI) during hospitalization for intracerebral hemorrhage. Emergent coronary angiography (CAG) revealed severe stenosis of the distal left circumflex coronary artery. We implanted a BMS to avoid long-term triple antithrombotic therapy. He received aspirin, clopidogrel, and rivaroxaban for 1 month and then received clopidogrel and rivaroxaban. Seventy days after BMS implantation, he developed AMI, and emergent CAG revealed occlusion of the BMS due to late stent thrombosis. After thrombus aspiration, intravascular ultrasound showed incomplete neointimal healing in the proximal portion of the stent and excessive neointimal proliferation in the distal portion of the stent. DCB angioplasty of the entire BMS was performed after scoring balloon pre-dilation. Seven months after BMS implantation, follow-up CAG revealed binary ISR. DCB angioplasty of the entire BMS was performed again after scoring balloon pre-dilation. Thirteen months after BMS implantation, follow-up CAG did not reveal recurrence of ISR.

<**Learning objective:** Drug-coated balloons (DCB) were ineffective when there was excessive neointimal proliferation accompanied by thrombosis, but effective in binary in-stent restenosis (ISR). DCB may be ineffective in early ISR after bare-metal stent implantations and when there is excessive neointimal proliferation accompanied by thrombosis. Since the safety and efficacy of DCB to treat excessive neointimal proliferation occurring with late stent thrombosis is unclear, further studies are needed.>

Introduction

Stent thrombosis (ST) after percutaneous coronary interventions (PCI) is a rare but serious life-threatening complication [1]. Pathological findings at the time of late ST (LST) after bare-metal stent (BMS) implantation include incomplete neointimal healing and diffuse in-stent restenosis (ISR) [1]. Although drug-coated balloons (DCB) are effective in the treatment of BMS restenosis, it is unclear whether DCB are effective when there is excessive neointimal proliferation accompanied by thrombosis [2]. We describe a rare case in which the first DCB angioplasty was ineffective when there was excessive neointimal proliferation occurring with LST; however, the second DCB angioplasty was effective in treating binary ISR in the chronic phase.

Case report

An 84-year-old man with diabetes mellitus developed ST elevation myocardial infarction (STEMI) during hospitalization for intracerebral hemorrhage (Fig. 1). He had a history of inferior STEMI and underwent implantation of a 3.0 × 20 mm BMS (Liberte, Boston Scientific, Nattick, MA, USA) in the middle right coronary artery five years previously. He was also diagnosed with atrial

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https://doi.org/10.1016/j.jccase.2019.04.007
1878-5409/

Fig. 1. The clinical course.
A, aspirin; C, clopidogrel; R, rivaroxaban; STEMI, ST elevation myocardial infarction; BMS, bare-metal stent; RCA, right coronary artery; LCX, left circumflex coronary artery; LST, late stent thrombosis; DCB, drug-coated balloon; ISR, in-stent restenosis.

fibrillation 2 years previously and was on anticoagulation therapy. Antithrombotic treatment with oral aspirin and rivaroxaban was discontinued after the diagnosis of intracerebral hemorrhage 10 days previously. Fortunately, the intracerebral hemorrhage was small, so anticoagulation therapy with 10 mg rivaroxaban was restarted 6 days previously.

However, he suffered continuous chest pain, and the electrocardiogram (ECG) showed ST-segment elevation in leads II, III, and aVF. We suspected very late ST of the BMS, which was implanted 5 years previously. Emergent coronary angiography (CAG) revealed a patent BMS and de novo severe stenosis of the distal left circumflex coronary artery (LCX) (Fig. 2A). The culprit lesion was treated by implantation of a 3.5 × 18 mm BMS (Integrity, Medtronic, Dublin, Ireland), because there was a high risk of bleeding with long-term triple antithrombotic therapy [3]. Intravascular ultrasound (IVUS) with the OptiCross system (Boston Scientific) showed good stent expansion and apposition, and the final CAG revealed good coronary blood flow (Fig. 2B). Although he received oral triple antithrombotic therapy with aspirin, clopidogrel, and rivaroxaban after PCI, he was discharged 8 days later without worsening bleeding.

Based on the consensus document [3], antithrombotic therapy was reduced to clopidogrel and rivaroxaban 1 month later. Seventy days after BMS implantation, he was admitted to our hospital for frequent angina attacks. Although his ECG showed no significant changes, the diagnosis of acute coronary syndrome (ACS) was confirmed by serum cardiac biomarker elevation. Emergent CAG revealed occlusion of the BMS in the distal LCX due to LST (Fig. 2C). Although some red thrombi were obtained by the first aspiration with a 6Fr Eliminate3 catheter (TERUMO, Aichi, Japan), IVUS showed good stent expansion and apposition, but incomplete neointimal healing and residual thrombi in the proximal portion of the stent (Fig. 2C and Supplementary Video 1). The thrombus aspiration was repeated several times, and some white thrombi were obtained. IVUS also revealed excessive neointimal proliferation at the distal portion of the stent (Fig. 2C and Supplementary Video 1). Since excessive neointimal proliferation was observed in a short time, we were concerned about binary restenosis. Therefore, we performed DCB angioplasty with a 3.5 × 20 mm SeQuent Please (B Braun, Melsungen, Germany) of the entire BMS after scoring balloon pre-dilation with a 3.5 × 13 mm NSE ALPHA (GOODMAN, Aichi, Japan). Final CAG and IVUS revealed an acceptable lumen diameter and good coronary blood flow (Fig. 2D and Supplementary Video 2). The same triple antithrombotic therapy was started again, with the addition of statin therapy (atorvastatin 5 mg/day), despite a low-density lipoprotein cholesterol of 60 mg/dL.

Seven months after BMS implantation, follow-up CAG and IVUS revealed severe ISR in the distal portion of the BMS, where excessive neointimal proliferation was observed at the time of the previous PCI (Fig. 2E and Supplementary Video 3). Although the ISR that occurred after the first DCB angioplasty was binary, the lesion was focal, so our PCI strategy was similar to the previous PCI strategy. The second DCB angioplasty of the entire BMS with a 3.5 × 20 mm SeQuent Please was performed after scoring balloon pre-dilation with a 3.25 × 13 mm NSE ALPHA. Final CAG and IVUS revealed an acceptable lumen diameter and good coronary blood flow (Fig. 2F and Supplementary Video 4). Cardiac events did not recur after the second DCB angioplasty. Furthermore, follow-up CAG 13 months after BMS implantation showed no recurrence of ISR (Fig. 2G).

Discussion

This case illustrates two important clinical issues. DCB may be ineffective in early ISR after BMS implantation and when there is excessive neointimal proliferation accompanied by thrombosis.

First, DCB may be ineffective in early ISR after BMS implantation. In our case, excessive neointimal proliferation with LST appeared at the portion where the plaque ruptured and caused STEMI. Coronary stenting causes a more intense and prolonged inflammatory state than ballooning alone, and neointimal proliferation after coronary stenting persists for at least 3 months [1,4]. Furthermore, PCI for unstable lesions causing ACS had a higher rate of restenosis than PCI for stable lesions [5]. In our case, the first DCB angioplasty to treat LST was performed 70 days after BMS implantation, when there was excessive neointimal proliferation. Thus, it was thought that the neointimal proliferative response was active at this time. In contrast, the neointimal proliferative response was inactive when the second DCB angioplasty was performed to treat ISR about 7 months after BMS implantation. Paclitaxel can inhibit arterial endothelial cells growth only for 2 weeks after DCB angioplasty [6]. Therefore, this interval is enough to treat inactive lesions but not enough to treat active lesions. According to optical coherence tomography (OCT)

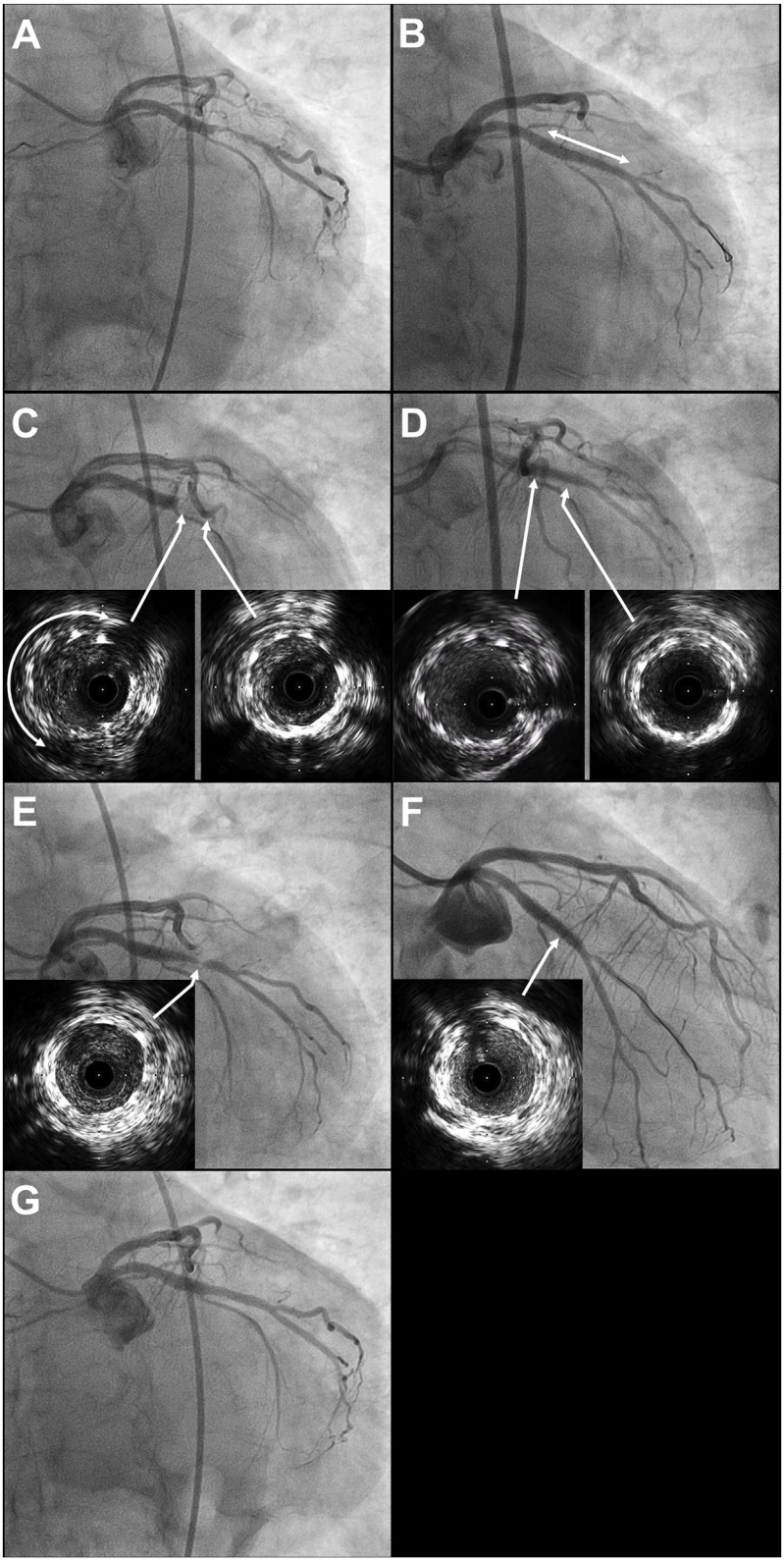

Fig. 2. Coronary angiograms and intravascular ultrasound (IVUS) images. (A) Coronary angiography (CAG) demonstrated severe stenosis and haziness of the distal left circumflex coronary artery (LCX) at the time of ST elevation myocardial infarction (STEMI). (B) CAG after bare-metal stent (BMS) implantation in the distal LCX (double arrow) demonstrated good coronary blood flow at the time of STEMI. (C) CAG demonstrated occlusion of the BMS due to late stent thrombosis (LST) 70 days after BMS implantation. IVUS after thrombus aspiration showed good stent expansion and apposition but incomplete neointimal healing with a massive thrombus (double arrow) in the proximal portion of the stent and excessive neointimal proliferation in the distal portion of the stent. (D) CAG and IVUS after the first drug-coated balloon (DCB) angioplasty of the BMS demonstrated acceptable luminal diameter and good coronary blood flow through the stent. (E) CAG demonstrated severe binary in-stent restenosis (ISR) in the distal portion of the stent on follow-up CAG seven months after BMS implantation. IVUS showed apposition and excessive intimal proliferation in this portion of the stent. (F) CAG and IVUS after the second DCB angioplasty to treat ISR demonstrated acceptable luminal diameter and good coronary blood flow through the stent. (G) CAG did not demonstrate ISR at follow-up CAG 13 months after BMS implantation.

studies, neointimal tissue with heterogeneous pattern on OCT might be ineffective to be treated by DCB angioplasty, and might be neointima having fibrin accumulation along with smooth muscle cells which appeared in neointima healing process [1,7]. Therefore, OCT examination may determine whether neointimal proliferative response is active or inactive, and OCT examination might predict ineffectiveness of the first DCB angioplasty and effectiveness of the second DCB angioplasty in our case. Thus, DCB may be ineffective in early ISR after BMS implantation, and there is the possibility that repeated DCB angioplasty may be required.

Second, DCB may be ineffective when there is excessive neointimal proliferation accompanied by thrombosis. Even if balloon angioplasty was performed at the site of a thrombotic lesion in the stent, many residual thrombi are left in the stent [8]. Thrombi attached to the neointima may inhibit absorption of paclitaxel into the vascular wall; therefore, DCB angioplasty may be ineffective in lesions with thrombosis. However, in a previous randomized trial (DEB-AMI; drug-eluting balloon in ST-segment elevation myocardial infarction), uncovered and malapposed stent struts were more frequently seen in patients with DCB plus BMS than in patients with BMS alone [9]. This indicates that DCB may not be fully effective in STEMI with high thrombus burden and that DCB may be useful for treating ISR with thrombosis. In a previous case report about the treatment of a patient presenting with very late ST with the use of a DCB, DCB angioplasty might be effective and considered in treatment for very late ST as a result of neoatherosclerosis [10]. In our case, both excessive neointimal proliferation in the distal stent and incomplete neointimal healing with a massive thrombus in the proximal stent were observed when LST occurred. Thus, DCB angioplasty might result in a beneficial effect on excessive neointimal proliferation, whereas it may have a harmful effect on incomplete neointimal healing. In fact, DCB angioplasty was ineffective when there was excessive neointimal proliferation, but did not worsen incomplete neointimal healing. We speculate that paclitaxel could not be absorbed into the vascular wall, because the lesion with incomplete neointimal healing had a massive thrombus at the time of the first DCB angioplasty to treat LST.

In conclusion, we describe a rare case in which the first DCB angioplasty was ineffective when there was excessive neointimal proliferation occurring with LST, but the second DCB was effective in treating binary ISR during the chronic phase. DCB angioplasty may be ineffective in early ISR after BMS implantation or when there is excessive neointimal proliferation accompanied by thrombosis. Even if DCB angioplasty is ineffective for initial ISR, DCB angioplasty may be effective later when there is recurrence of ISR because neointimal proliferation may be less active or there may be fewer thrombi in the stent. Furthermore, DCB angioplasty does not need additional stents, so that DCB angioplasty can be performed multiple times unlike stenting. However, it is unclear whether DCB angioplasty for excessive neointimal proliferation accompanied by thrombosis is effective and safe, so further studies are needed.

Conflict of interest

The authors declare that there is no conflict of interest.

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.2019.04.007.

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