CASE REPORT

Late Stent Thrombosis After Drug-Coated Balloon Coronary Angioplasty for In-Stent Restenosis
A Case Report

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Summary
A 41-year-old woman with chest pain for 6 hours was admitted to our chest pain center, presenting with acute myocardial infarction. Coronary angiography showed acute total occlusion in the proximal left anterior descending artery due to late stent thrombosis. After thrombus aspiration and intracoronary administration of 0.5 mg tirofiban, repeated angiography showed that no obvious residual stenosis remained. The patient underwent drug-coated balloon angioplasty 69 days ago and was then administered dual antiplatelet treatment (aspirin and clopidogrel) uninterruptedly. Genetic testing found that both cytochrome P450 2C19 (CYP2C19) (G681A) and glycoprotein Ia (GPla) (C807T, G873A) were hybrid mutant types, demonstrating that the patient was possibly resistant to clopidogrel and aspirin simultaneously. Thus, clopidogrel was replaced by ticagrelor and no more cardiovascular adverse events occurred during the 2-year follow-up.

Key words: Coronary artery disease, Gene mutation, Antiplatelet strategy, Myocardial infarction

The introduction of stents is an important step forward in our ability to treat coronary artery diseases. However, a newly emerging problem - in-stent restenosis (ISR) - is becoming apparent. ISR is defined as > 50% stenosis of a previously stented segment.1 ISR occurs in up to 30% of all patients treated with bare-metal stents.2 Although the development of drug-eluting stents (DES) has decreased ISR rates, at least 5-10% of patients suffer from DES ISR and require target vessel revascularization.3

Several established approaches have been applied in the management of ISR. Drug-coated balloon (DCB) angioplasty is an emerging technology that has been tested for ISR treatment.4 As the DCB delivers the antiproliferative drugs to the area of ISR, avoiding the introduction of an additional stent layer, treatment with DCB for ISR should have faster and safer vessel healing and a shorter dual antiplatelet therapy (DAPT) regimen.5 We report the case of a female patient who underwent DCB angioplasty because of recurrent ISR and late stent thrombosis that occurred after 70 days, despite uninterrupted DAPT.

Case Report
The patient’s history indicated that she did not have hypertension or diabetes mellitus. She underwent the first percutaneous coronary intervention (PCI) at the age of 37 years. Coronary angiography was performed because of unstable angina (III, Braunwald Classification), and showed <90% stenosis on the proximal left anterior descending artery (LAD) and >80% stenosis in the ostium of the first diagonal branch (D1). For treatment, a double-kissing-crush (DK-crush) stenting technique was used. A 2.5 × 15 mm DES (sirolimus) was first implanted in the ostium of D1 to the LAD and then another 3.25 × 25 mm DES (sirolimus) was implanted in the proximal LAD crossing the ostium of D1. Two years later, this patient was admitted to our hospital because of paroxysmal chest tightness for 3 days. Coronary angiography showed that the LAD was occluded in the proximal stent. To treat the ISR, PCI was performed again, and a 3.0 × 24 mm DES was implanted in the proximal LAD inside the first 3.25 × 25 mm DES. The patient was admitted to our hospital for the third time about 1 year after the second PCI, because
of chest tightness and chest pain after exercise for 1 month. Coronary angiography showed 95% stenosis in the proximal LAD, indicating that recurrent ISR had occurred. As the DES was used to treat ISR the previous time and two layers of stent remained in the proximal LAD, DCB angioplasty was preferred this time. After predilation with a 2.5 × 20 mm semi-compliant balloon and a 3.0 × 10 mm flextome cutting balloon, the ISR lesion was treated with a 3.0 × 30 mm DCB (paclitaxel, 8 atm, 60 seconds). Repeated angiography showed no residual stenosis in the stent (Figure 1A-C). The patient was on DAPT with aspirin and clopidogrel after discharge.

The patient presented to our chest pain center because of sustained chest pain for 6 hours. The electrocardiogram showed ST-segment elevation in leads V1-V3. She was diagnosed with acute ST-segment elevation myocardial infarction (STEMI). Coronary angiography showed acute total occlusion of the proximal LAD due to late stent thrombosis. After thrombus aspiration and intracoronary administration of 0.5 mg tirofiban, repeated angiography showed that no obvious residual stenosis remained in the proximal LAD (Figure 1D and E). To uncover why late stent thrombosis occurred in this patient after DCB angioplasty, we tested the aspirin resistance-related gene (cyclooxygenase-1 [COX1] and GPIa) polymorphism and the clopidogrel resistance-related gene (CYP2C19) polymorphism. Genetic testing showed that the patient was wild-type for COX1 polymorphism, but mutant-hybrid type for both GPIa (C807T, G873A) polymorphism and CYP2C19 (G681A) polymorphism, suggesting that she was at high risk of both aspirin resistance and clopidogrel resistance. Then, the oral P2Y12 inhibitor was switched from clopidogrel to ticagrelor and the DAPT duration was prolonged to 12 months. No stent thrombosis or other adverse cardiovascular events occurred again during the 2 years of follow-up. The detailed antiplatelet regimen is shown in Figure 2.

Discussion

ISR rates range from 5% to 10% and remain a therapeutic challenge, although great improvements have been achieved in second-generation DESs.\(^5\)\(^\) The mechanism of ISR is complicated and multiple factors, including biological, mechanical, patient-related, and operator-related factors, contribute to the occurrence and development of ISR.\(^5\)\(^\) As the patient underwent the first PCI using the DK-crush stenting technique owing to bifurcation lesions, stent underexpansion or stent malapposition might have been the main cause of ISR, which should have been but was not evidenced by intracoronary imaging (intravascular ultrasound or optical coherence tomography). ISR occurred again only 1 year after the second stenting. The accelerated formation of neoatherosclerosis should be related to the double layers of stents.

Although the value of DCB angioplasty in the treat-
ment of new lesions needs to be studied further, the effectiveness of DCB angioplasty in the treatment of ISR has been confirmed in several studies.3,4 Compared to new-generation DESs, DCB angioplasty has multiple advantages in the treatment of ISR.5 The surface area of the balloon is much larger than the adherence area of the stent metal beam, which can deliver more antiproliferative drugs to the vessel wall and release antiproliferative drugs more evenly, avoiding “blind areas.” The onset and lasting time of the residual drug is reasonable, which not only inhibits the proliferation of the intima but also facilitates the endothelialization of the damaged part of the wall. DCB angioplasty avoids the coverage of new metal beams and helps to deal with subsequent possible lesions. The DAPT duration can be shortened, reducing the risk of bleeding. In the present case, another DES was implanted to treat the ISR, but recurrent ISR occurred about 1 year later. Then, DCB angioplasty was performed to cope with the problem.

The choice of antiplatelet strategy after DCB angioplasty is currently controversial. Current manufacturers advise 3 months of DAPT after DCB angioplasty. Some studies advise that DAPT be administered for at least 6 months after DCB treatment.6 The “Chinese Expert Consensus for Clinical Application of Drug-Coated Balloons (2016)” recommended that when DCB angioplasty is used alone, the DAPT duration should be 1-3 months. Definitive conclusions on DCB angioplasty cannot be made because of a shortage of related studies. Stent thrombosis after the treatment of ISR with DCB angioplasty is rare.7 Although the doctor insisted that the patient take oral aspirin and clopidogrel after DCB treatment, she suffered from STEMI due to late stent stenosis. Further examinations indicated the patient might have antiplatelet resistance due to gene mutations. Several COX1 mutations and aspirin resistance were analyzed previously. The mutation A1676G seemed to be associated significantly with aspirin resistance, which might be attributed to the increased expression of COX1. The average frequency of G alleles is about 40%.8 GP1a mutations - C807T (frequency: 37%) and G873A (frequency: 37%) - might also lead to aspirin resistance, which can be explained by changes in platelet adhesion.9 Common genetic variations in CYP2C19 (G681A and G636A) result in a premature stop codon and lead to a loss of the functional protein. Both the alleles reduce the production of clopidogrel - an active metabolite - resulting in clopidogrel resistance. The minor allele frequency of the CYP2C19 G681A polymorphism is 31% in East Asians and 32.5% in South Asians. The minor allele frequency of the CYP2C19 G636A polymorphism is 6.3% in East Asians and 0.4% in South Asians.10

Conclusion
DCB angioplasty is used widely to treat ISR. This case indicates that a sufficient and effective DAPT is necessary after DCB angioplasty. For patients at a high risk of thrombus, potent P2Y12 inhibitors should first be considered.

Disclosure
Conflicts of interest: The authors declare that they have no competing interests associated with this report.

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