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Case Report

Repetitive early stent thrombosis in a patient with the CYP2C19*3/*3 genotype

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Summary A 45-year-old man presented with acute inferior myocardial infarction and underwent emergent coronary angiography (CAG). CAG revealed total occlusion of both the proximal right coronary artery (RCA) and distal left circumflex artery, and two bare-metal stents were deployed in the RCA. After the procedure, dual antiplatelet therapy (DAT) with 100 mg aspirin and 75 mg clopidogrel daily were given as usual, however, stent thrombosis occurred three times and he underwent repeat interventions. To investigate the cause of repeated stent thrombosis, the platelet function during DAT was measured. The result showed that he did not achieve an adequate antiplatelet effect.

Clopidogrel is a prodrug that requires biotransformation by cytochrome P450 (CYP) enzyme in the liver. Recently, the carriers of CYP2C19*2 or *3 null-of-function allele, have been shown to demonstrate an increased risk of cardiovascular events, including stent thrombosis, compared with non-carriers. This patient carried the CYP2C19*3/*3 genotype.

This is the first report of repetitive stent thrombosis in a poor metabolizer carrying two loss-of-function alleles (CYP2C19*3/*3).

Introduction

Dual antiplatelet therapy (DAT) with 100 mg aspirin and 75 mg clopidogrel daily is the standard treatment to prevent stent thrombosis [1], however, some patients do not

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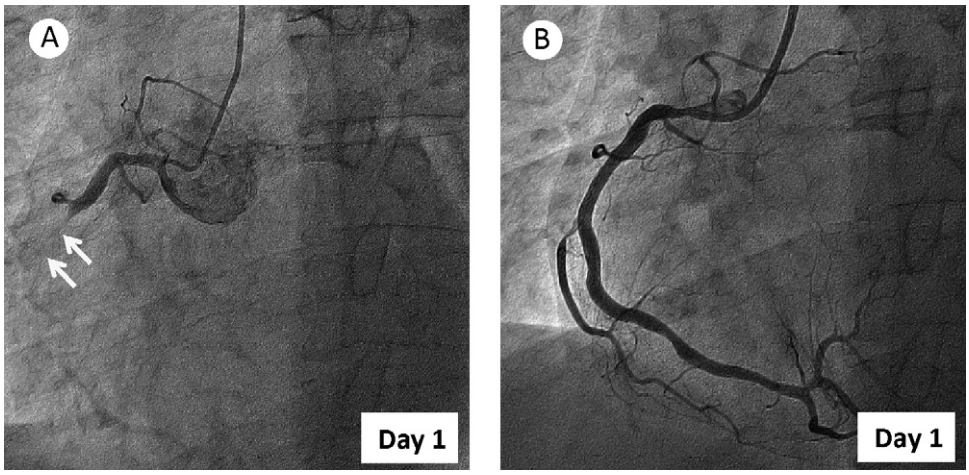

Figure 1 (A) Total occlusion of the proximal right coronary artery (arrow). (B) Post-stent deployment, with excellent results.

achieve an adequate antiplatelet effect with clopidogrel, which may be associated with stent thrombosis. Because clopidogrel is a prodrug that requires biotransformation to an active metabolite by cytochrome P450 (CYP) enzyme in the liver, CYP polymorphisms are reportedly associated with high on-clopidogrel platelet reactivity. Specifically, carriers of the CYP2C19*2 or *3 allele, with null functions, have been shown to demonstrate a higher rate of cardiovascular events, including stent thrombosis, than non-carriers [2].

Case report

In February 2009, a 45-year-old man was admitted to the emergency department complaining of sudden left-sided chest and shoulder pain with nausea and cold sweats. His only cardiac risk factor was dyslipidemia. An electrocardiogram (ECG) showed ST segment elevation in the inferior leads and echocardiogram revealed reduced wall motion in the inferior wall. He was diagnosed with acute inferior myocardial infarction and underwent emergent coronary angiography (CAG). CAG revealed total occlusion of both the proximal right coronary artery (RCA) and distal left circumflex artery (Fig. 1A). Two 3.0×18 mm and 3.0×12 mm Driver stents (Medtronic, Minneapolis, MN, USA) were deployed in the culprit lesion in the RCA, with excellent results (Fig. 1B). Before percutaneous coronary intervention (PCI), 200 mg aspirin and 300 mg clopidogrel were given as loading, followed by 100 mg aspirin and 75 mg clopidogrel daily as maintenance doses. Three days after first PCI, ECG revealed the recurrence of ST segment elevation in the inferior leads, and he immediately underwent emergent CAG. Angiography revealed total occlusion of the proximal RCA due to early stent thrombosis (Fig. 2A). Balloon angioplasty was performed several times, and a 3.0×24 mm Driver stent was deployed again, but thrombi immediately occurred in the stents. Finally, intra-aortic balloon pumping (IABP) was employed, and adequate antegrade coronary flow was achieved after repeated balloon angioplasty. Although continuous infusion of heparin and administration of warfarin were added after re-PCI to inhibit thrombogenesis, stent thrombosis recurred 5 days after the second PCI (Fig. 2B). Thrombectomy and a 3.5×23 mm Driver stent deployment were performed with IABP. Unfortunately, he developed chest discomfort with increased cardiac enzymes 13 days after the third PCI. CAG revealed a third stent thrombosis (Fig. 2C) and thrombectomy, and 3.5×33 mm and 3.5×23 mm Cypher stents (Cordis, Miami Lakes, FL, USA) were deployed. After this procedure, DAT with 100 mg aspirin and 75 mg clopidogrel was changed to triple antiplatelet therapy (TAT) with 200 mg aspirin, 75 mg clopidgrel, and 200 mg cilostazol daily. There was no further stent thrombosis and no stent restenosis for 6 months (Fig. 2D).

To examine the cause of repeated stent thrombosis, the platelet function during DAT was measured using a light transmittance aggregometer (MCM HEMA TRACER 313; PAM12C; LMS Inc., Japan) with a strong suspicion of high platelet reactivity after repeated PCI. As a result, 20 μmol/L adenosine diphosphate-induced platelet aggregation was 71% at maximum, and showed 6269 aggregation units $\times$ min from the area under the platelet aggregation curve. These findings revealed the reduced antiplatelet efficacy of clopidogrel. To elucidate the causes of the reduced antiplatelet efficacy, we performed CYP2C19 genotype analysis around the same time that we measured the platelet function. He had homogenous variants at exon 4 of CYP2C19*3/*3, which showed him to be a poor metabolizer. In this case, clopidogrel hyporesponsiveness by CYP2C19 polymorphisms may be one of the reasons for repeated stent thrombosis.

Discussion

The causes of early stent thrombosis are multifactorial, such as residual target lesion thrombus or dissection, stasis, stent underexpansion, unstable hemodynamics, dehydration, heparin-induced thrombocytopenia [3] and clopidogrel hyporesponsiveness [4]. Although intravascular ultrasound (IVUS) was not used, there was no thrombus or dissection and an adequate vessel diameter was obtained by angiographic evaluation. His hemodynamics were stable and dehydration did not occur in the course of treatment. There was no decrease in the number of platelets and no evidence of embolism during the treatment period, therefore, we thought the possibility of heparin-induced

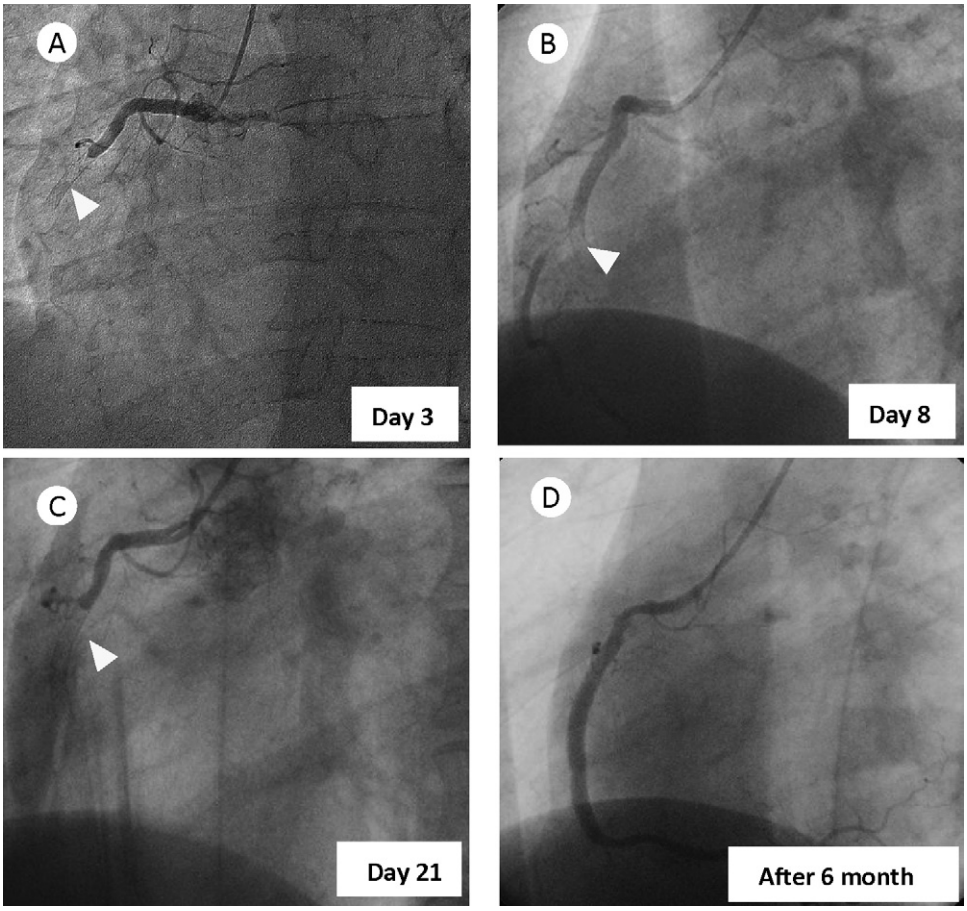

Figure 2 (A)—(C) Repeated stent thrombosis (arrowhead). (D) No stent restenosis after repeat PCI for 6 months.

thrombocytopenia was very low. For these reasons, we thought that high on-clopidogrel platelet reactivity played a key role in repeat stent thrombosis. Similarly, the mechanisms of a poor response to clopidogrel are multifactorial, such as age, renal failure, body mass index, diabetes, high plasma fibrinogen, lack of adherence, and CYP polymorphisms [5—7]. In this case, the level of plasma fibrinogen was normal and the other factors seemed to be inapplicable. Hence, we strongly suspected that the cause of high on-clopidogrel platelet reactivity was CYP polymorphisms.

To the best of our knowledge, this is the first report of repetitive stent thrombosis in a poor metabolizer carrying two loss-of-function alleles of CYP2C19. The rate of poor metabolizers and CYP2C19*3/*3 carrier is reportedly about 19% and 1%, respectively, in Japanese patients with coronary heart disease. We reported that poor metabolizers show high on-clopidogrel platelet reactivity compared with extensive metabolizers carrying normal function alleles, or intermediate metabolizers carrying one loss-of-function allele [8]. Although it was reported that there was no difference in clopidogrel reactivity between CYP2C19*2 and CYP2C19*3 carriers [9], the functional difference between *2 and *3 is still obscure in clinical practice such as the occurrence of cardiovascular events, including stent thrombosis. Further studies are needed to clarify the meaning of CYP2C19*3 carrier.

Cilostazol is a potent oral antiplatelet agent inhibitor of type III phosphodiesterase, a mechanism different from adenosine diphosphate receptor antagonists. It was reported that TAT seemed to be more effective in preventing thrombotic complications after stenting than DAT and might be applied in patients with high risk of stent thrombosis [10]. Although the platelet function was not measured during TAT in this case, the platelet function might be inhibited by the use of cilostazol via a different antiplatelet mechanism.

We selected a sirolimus-eluting stent at the last PCI, however, the use of drug-eluting stent should have been avoided under the high-risk situation of stent thrombosis or high platelet reactivity. It would be difficult to fully explain the mechanism of the repetition of stent thrombosis without IVUS observation because we could not promise the absence of dissection and stent underexpansion. IVUS should be used to evaluate the intravascular lumen and stent when stent thrombosis occurs.

Conclusion

In this case report, we described a patient with early stent thrombosis with the CYP2C19*3/*3 genotype. When stent thrombosis occurs, evaluation of the platelet function is recommended if possible, however, it is impossible to measure

platelet reactivity at all sites. It may be a useful procedure to add another antiplatelet agent, for example, cilostazol, to DAT in cases of suspected high on-treatment platelet reactivity.

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References

[1] Kushner FG, Hand M, Smith Jr SC, King 3rd SB, Anderson JL, Antman EM, Bailey SR, Bates ER, Blankenship JC, Casey Jr DE, Green LA, Hochman JS, Jacobs AK, Krumholz HM, Morrison DA, et al. Focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2009;120:2271—306.

[2] Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias W, Braunwald E, Sabatine MS. Cytochrome P-450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360:354—62.

[3] Hussain F, Philipp R, Zieroth S. HITT and stent thrombosis: a ''clinical'' diagnosis not to be missed. Int J Cardiol 2009;133:e11—3.

[4] Holmes Jr DR, Kereiakes DJ, Garg S, Serruys PW, Dehmer GJ, Ellis SG, Williams DO, Kimura T, Moliterno DJ. Stent thrombosis. J Am Coll Cardiol 2010;56:1357—65.

[5] Ang L, Palakodeti V, Khalid A, Tsimikas S, Idrees Z, Tran P, Clopton P, Zafar N, Bromberg-Marin G, Keramati S, Mahmud E. Elevated plasma fibrinogen and diabetes mellitus are associated with lower inhibition of platelet reactivity with clopidogrel. J Am Coll Cardiol 2008;52:1052—9.

[6] Geisler T, Grass D, Bigalke B, Stellos K, Drosch T, Dietz K, Herdeg C, Gawaz M. The Residual Platelet Aggregation after Deployment of Intracoronary Stent (PREDICT) score. J Thromb Haemost 2008;6:54—61.

[7] Serebruany V, Cherala G, Williams C, Surigin S, Booze C, Kuliczkowski W, Atar D. Association of platelet responsiveness with clopidogrel metabolism: role of compliance in the assessment of ''resistance''. Am Heart J 2009;158:925—32.

[8] Yamamoto K, Hokimoto S, Chitose T, Morita K, Ono T, Kaikita K, Tsujita K, Abe T, Deguchi M, Miyagawa H, Saruwatari J, Sumida H, Sugiyama S, Nakagawa K, Ogawa H. Impact of CYP2C19 polymorphism on residual platelet reactivity in patients with coronary heart disease during antiplatelet therapy. Impact of CYP2C19 polymorphism on residual platelet reactivity in patients with coronary heart disease during antiplatelet therapy. J Cardiol 2011;57:194—201.

[9] Hwang SJ, Jeong YH, Kim IS, Koh JS, Kang MK, Park Y, Kwak CH, Hwang JY. The cytochrome 2C19*2 and *3 alleles attenuate response to clopidogrel similarly in East Asian patients undergoing elective percutaneous coronary intervention. Thromb Res 2011;127:23—8.

[10] Chen KY, Rha SW, Li YJ, Poddar KL, Jin Z, Minami Y, Wang L, Kim EJ, Park CG, Seo HS, Oh DJ, Jeong MH, Ahn YK, Hong TJ, Kim YJ, et al. Triple versus dual antiplatelet therapy in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Circulation 2009;119:3207—14.