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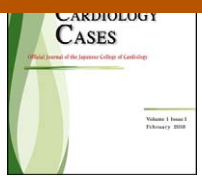

Case Report

Repeated intra-stent thrombus formation in a patient with acute coronary syndrome due to poor responsiveness to clopidogrel may be associated with cytochrome P-450 2C19*2 polymorphism

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Summary A drug-eluting stent was implanted at the culprit lesion in a 65-year-old man with acute coronary syndrome. Nine days after the procedure, he suffered stent thrombosis, and a bare-metal stent was subsequently implanted. Twelve days after this second procedure, a follow-up angiogram showed a newly emerged thrombus at the site of stent implantation. Although the patient had continued dual anti-platelet therapy with aspirin and clopidogrel since the first procedure, platelet optical aggregation test showed no inhibition of aggregation. Further, genetic analysis revealed him to be homozygous for the CYP2C19*2 polymorphism. This case suggests that the mechanism of stent thrombosis, while multi-factorial, is affected greatly by crossover of poor responsiveness to clopidogrel due to the CYP2C19*2 polymorphism.

Introduction

Dual anti-platelet therapy with aspirin and clopidogrel is routinely administered after coronary stent implantation including drug-eluting stents (DES) to stave off thrombotic events. Despite this treatment, however, many patients with DESs still experience thrombotic and ischemic events. Several recent studies have shown that poor or non-responsiveness to clopidogrel is strongly associated with stent thrombosis and poor clinical outcome in patients with DESs [1,2].

Genetic polymorphisms may play a pivotal role in determining patient responsiveness to clopidogrel. In particular,

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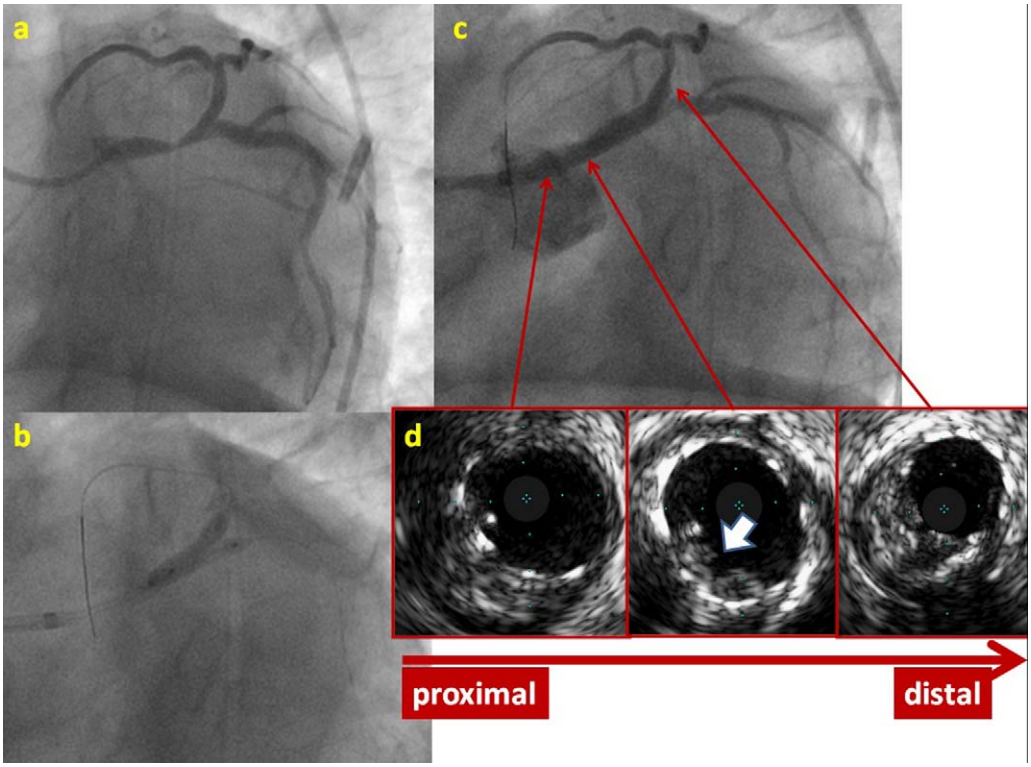

Figure 1 (a) A coronary angiogram showed severe stenosis in the left main trunk (LMT). (b) A 3.5 × 23-mm stent (Promus™, Boston Scientific Corporation, Natick, MA, USA) was implanted at 12 atm, and we performed kissing balloon dilatation. (c) After kissing balloon dilation, plaque prolapse appeared in the proximal site of the LMT stent. (d) Intravascular ultrasound examination revealed plaque prolapsed in the 6—8 o'clock direction (plaque prolapse indicated by white arrow).

the 2C19*2 allelic variant (681A allele) polymorphism of cytochrome P450 (CYP) is a common genetic functional variant believed to be an important contributor to the wide inter-individual variability in the anti-platelet effect of clopidogrel [3—6].

Here, we report a patient with the CYP2C19*2 polymorphism who suffered from repeated intra-stent thrombus formation, including stent thrombosis, caused by poor responsiveness to clopidogrel due to this polymorphism and demonstrated by the serial change in platelet aggregation test.

Case report

A 65-year-old Japanese man, who had reported experiencing chest pain when exerting himself on 26 April 2010, experienced severe chest pain and dyspnea on 28 April and was admitted to the emergency unit of our hospital. A electrocardiogram demonstrated ST segment elevation in aVR, aVL, and V1—V4 leads and depression in the II, III, aVF, V5, and V6 leads, and an echocardiogram showed severe hypokinesis in the anterior and lateral regions. Laboratory tests revealed the following: white blood cell count, 11,700/μl; aspirate aminotransferase, 43 IU/l; lactate dehydrogenase, 371 mequiv./l; creatine kinase, 313 mequiv./l; C-reactive protein, 0.13 mg/dl; glucose, 122 mg/dl, and troponin I, 2.890 mg/ml. Given that the patient's oxygen saturation was 87% even after being placed on 7 l of oxygen administered via a reservoir mask, we promptly performed intubation and supported him via a mechanical ventilator. Emergent coronary angiography (CAG) showed a severe stenosis in the left main trunk (LMT), but no significant stenosis in the right coronary artery (Fig. 1a). Because the patient's hemodynamic status was unstable, we promptly inserted an intra-aortic balloon pump (IABP) to stabilize it. We then performed percutaneous coronary intervention (PCI) for the LMT to the left anterior descending artery (LAD) with balloon inflation, implanted a 3.5 × 23-mm DES (Promus™, Boston Scientific Corporation, Natick, MA, USA) guided by intravascular ultrasound (IVUS; EagleEye™; Volcano Therapeutic Inc., Tokyo, Japan) and performed kissing balloon dilatation (Fig. 1b). Given that the angiogram showed plaque prolapse in stent site (Fig. 1c and d), we performed post-dilatation with a 3.5 × 15-mm balloon (Hiryu™, Terumo, Tokyo, Japan) up to only 6 atm to compress prolapsed intra-stent plaques, as high-pressure additional ballooning might induce much larger plaque prolapse. We confirmed reduction of the prolapse area using CAG and IVUS (minimum stent area was 7.0 mm^2), and then finished the procedure.

A loading dose of clopidogrel (300 mg) was administered to the patient immediately after the procedure, after which he received a maintenance dose of clopidogrel (75 mg/day) and aspirin (100 mg/day). The patient was weaned from the IABP after seven days and the ventilator after eight.

However, nine days after the initial procedure, the patient complained of severe chest pain, and the electrocardiogram showed ST segment elevation in aVR, aVL,

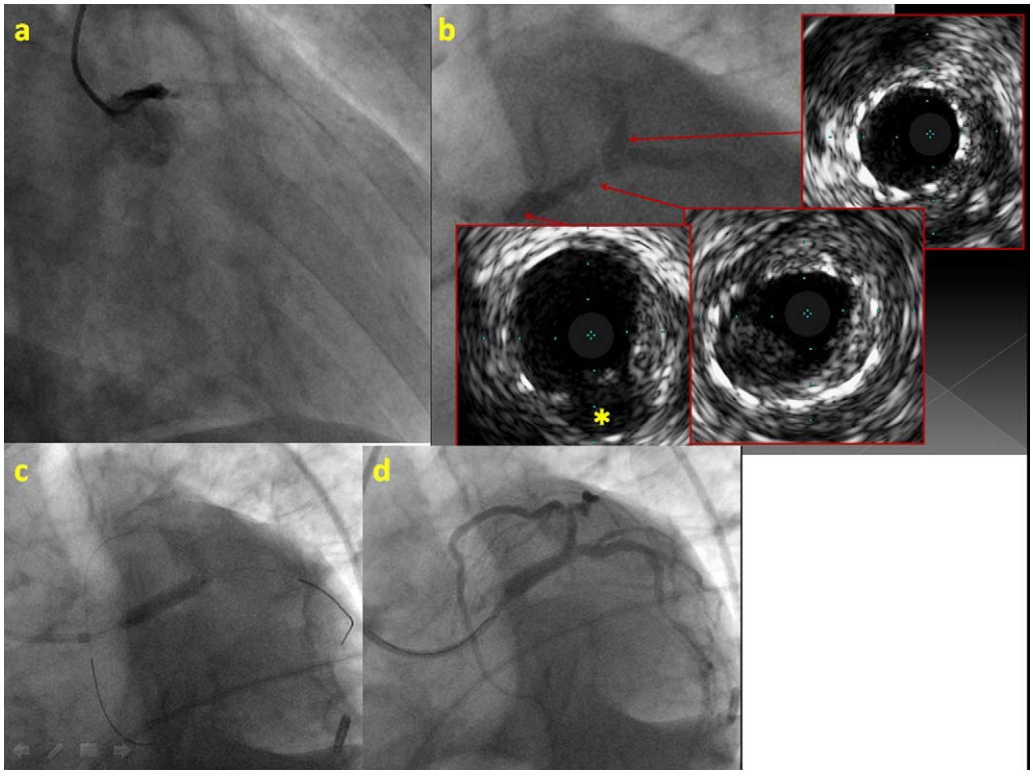

Figure 2 (a) A coronary angiogram showed stent occlusion in the stent site. (b) After aspiration of the thrombus, intravascular ultrasound revealed intra-stent thrombus localized in the left main trunk (LMT) site and malapposition (*) at the stent proximal edge. (c) A 4.0 × 20-mm bare-metal stent (Liberte™, Boston Scientific Corporation, Natick, MA, USA) was deployed at the LMT, and post-dilatation was performed using a 5.0 × 10-mm non-compliant balloon up to 16 atm. (d) A final angiogram showed good dilatation.

V1—V4 leads, and depression in II, III, aVF, V5, 6 leads. We performed an emergent angiogram on suspicion of subacute stent thrombosis, and the second CAG showed total occlusion of the stent site in the LMT (Fig. 2a). After IABP insertion, we aspirated the thrombus using a thrombi-extraction catheter (Thrombuster III GR™; Kaneka, Osaka, Japan). After coronary flow was regained to Thrombolysis In Myocardial Infarction 2 flow, we performed IVUS and found an intra-stent thrombus and strut mal-apposition at the proximal edge of the stent, which had not been noted after the first procedure (Fig. 2b). We implanted a 4.0 × 20-mm bare-metal stent (BMS; Liberte™; Boston Scientific Corporation) to cover the mal-apposition at the proximal edge of the previously inserted stent without crossing over the ostium of circumflex and performed post-ballooning with a 5.0 × 10-mm non-compliant balloon (Hiryu™) at 16 atm (Fig. 2c). Subsequent IVUS revealed good dilatation and apposition of the BMS. And also, a final angiogram showed good luminal dilatation (Fig. 2d).

Two days after the second PCI, the patient's hemodynamics stabilized, and he was weaned off of IABP. Ten days later, we performed a follow-up CAG (Fig. 3a), which revealed a newly emerged mobile thrombus in the middle of the stent site. We then aspirated the thrombus using a 5-Fr catheter (Hertrail™, Terumo) and confirmed size reduction via IVUS and CAG (Fig. 3b).

We initially suspected that the repeated intra-stent thrombus formation, including stent thrombosis, was due to heparin-induced thrombocytopenia (HIT). However, no HIT-associated immunoglobulins were detected. We then suspected poor responsiveness to clopidogrel as the cause of stent thrombosis and conducted a platelet aggregation test and genetic examination. Results of the aggregation test showed normal aggregation with 3 μg ADP (Fig. 4a), judged as a non-responder to dual antiplatelet therapy, and the genetic examination showed the patient to be homozygous for the CYP2C19*2 polymorphism. We changed the antiplatelet regimen to aspirin 100 mg + ticlopidine 200 mg + cilostazol 200 mg/day. A follow-up platelet aggregation test conducted after starting this new regimen showed good inhibition with 3 μg ADP (Fig. 4b), and 23 days after the second PCI, follow-up CAG showed disappearance of the stent thrombus.

Genetic analysis of patients with DES thrombosis (experience at two hospitals)

From January 2009 to April 2010, 532 patients were implanted DESs at Hyogo Prefectural Awaji Hospital and Kobe University Hospital. Of these 532 patients, six presented with DES thrombosis. On examining the genetic test results of five patients with stent thrombosis, we found that three were homozygous for CYP2C19*2, one was heterozygous, and one was a non-carrier. Details of these are described in Table 1.

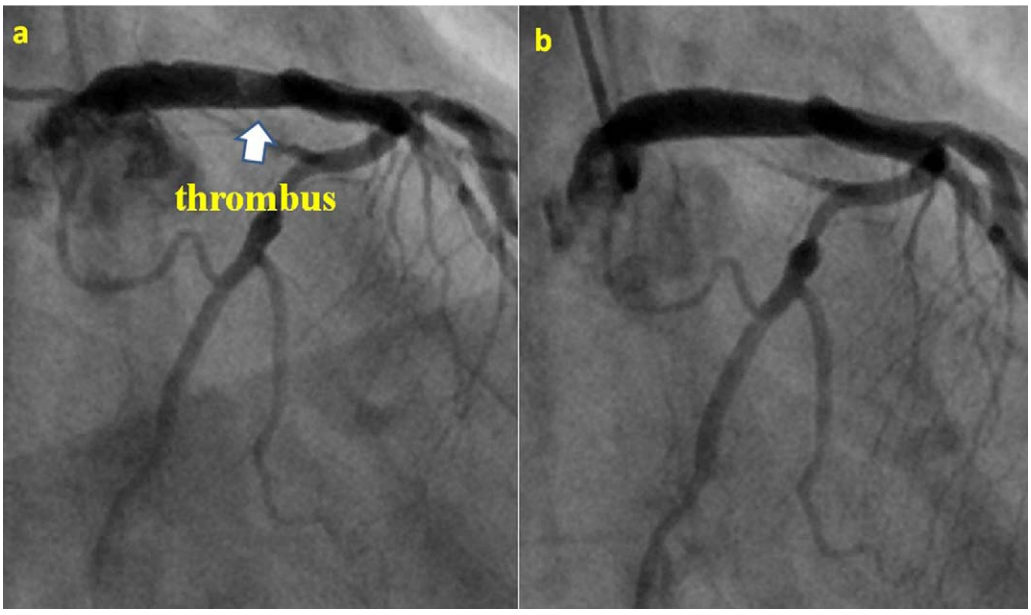

Figure 3 (a) Twelve days after the second percutaneous coronary intervention, an intra-stent thrombus was noted in the middle of the stent (white arrow). (b) After switching the patient from clopidogrel to ticlopidine, the thrombus disappeared.

Table 1 The characteristic data of the patients with drug-eluting stent thrombus.

Case	Age	Sex	Duration after PCI	Stent size	Risk factors of stent thrombosis	CYP2C19*2 polymorphism
1	65	M	8 days	EES 2.5 mm × 23 mm	ACS, stent undersizing, uncovered vulnerable plaque	Homozygous
2	56	M	5 days	SES 2.5 mm × 23 mm, 2.5 mm × 15 mm	ACS, low ejection fraction, stent under-expansion	Homozygous
3	66	M	5 days	PES 3.0 mm × 20 mm	Low ejection fraction, malapposition	Heterozygous
4	75	F	2 months	SES 3.0 mm × 28 mm, 2.5 mm × 18 mm	Crush stent (2 stents)	Homozygous
5	71	M	5 days	PES 2.5 mm × 20 mm	Under expansion, post rotablator	Non carrier

ACS, acute coronary syndrome; F, female; M, male; PCI, percutaneous coronary intervention; EES, everolimus-eluting stent; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent.

Discussion

Here, we reported a patient with the CYP2C19*2 polymorphism who suffered from repeated intra-stent thrombus formation, including stent thrombosis, caused by poor responsiveness to clopidogrel. Our observation suggests that genetics-induced poor responsiveness to clopidogrel may affect intra-stent thrombus formation and, when combined with other risk factors, increase a patient's likelihood of developing stent thrombosis.

While a rare complication, stent thrombosis is a catastrophic adverse event. Previous reports highlighted several factors associated with an increased risk of stent thrombosis, including the details of the PCI procedure (stent mal-apposition or under-expansion, number of implanted stents, stent length, persistent slow coronary blood flow, presence of dissections), patient and lesion characteristics, stent design, and premature cessation of anti-platelet drugs [7,8]. In this case, several considerable risk factors for stent thrombosis were observed: namely acute coronary syndrome, an implanted DES, relatively undersized stent in comparison with the vessel size, and uncovered vulnerable plaque. In this case, however, despite the fact that the minimal stent area was over 7 mm^2 after the first PCI, and that these risks had been almost completely resolved after the second PCI, the patient still experienced sub-acute stent thrombosis, and an intra-stent thrombus formed repeatedly over a short period. Because the patient continued to show

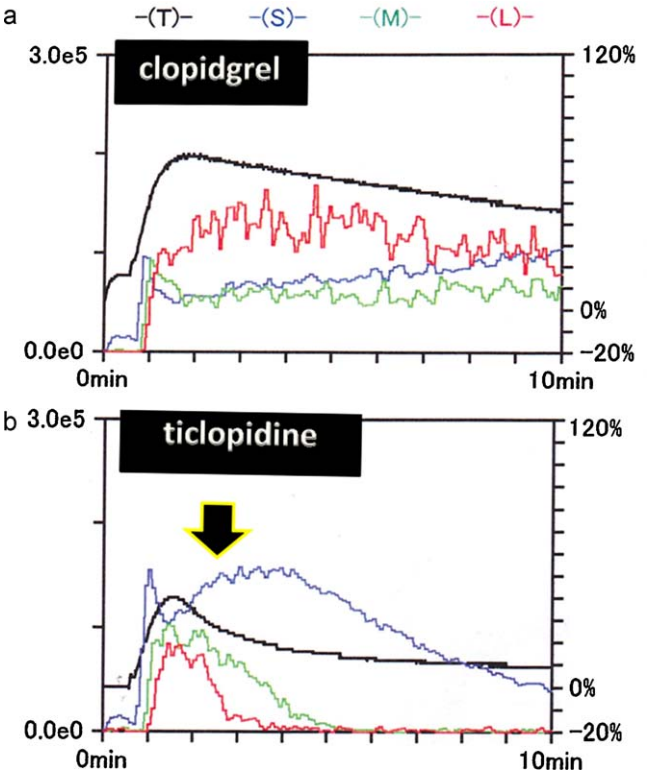

Figure 4 Aggregation test stimulated with 3 μmol adenosine 5′ diphosphate (ADP). (a) Platelet second-wave aggregation was not inhibited when receiving clopidogrel. (b) Second-wave aggregation was well inhibited when receiving ticlopidine and cilostazol (black arrow).

normal platelet aggregation despite receiving dual anti-platelet therapy with aspirin and clopidogrel, we switched the clopidogrel for ticlopidine and added cilostazol, suspecting clopidogrel resistance. After this change, platelet aggregation was inhibited, and no more intra-stent thrombi formed. This finding suggests that stent thrombosis occurs mainly due to technical factors, but may be affected greatly by the crossover of poor responsiveness to clopidogrel.

Recently, genetic polymorphisms have been implicated as causes of clopidogrel resistance. The CYP2C19*2 polymorphism is a common genetic functional variant and has been the target of much investigation as the cause of impaired platelet inhibition in patients receiving clopidogrel [3—6]. This polymorphism has also been associated with high on-treatment platelet reactivity after administration of clopidogrel [4]. Other studies have demonstrated a significant association between CYP2C19*2 carriers and an increased risk of stent thrombosis following coronary stent implantation [5]. Although the incidence of the CYP2C19*2 polymorphism is markedly higher in Asian populations, including Japanese, than Western populations, few studies have investigated the association between stent thrombosis and CYP2C19*2 polymorphisms among Japanese. At our two institutions, we encountered six patients with DES thrombosis, all receiving dual anti-platelet therapy with clopidogrel. Of the six patients, five patients were genotyped, and, four (80%) subsequently found to be *2 carriers (three homozygous and one heterozygous). Although this analysis was small and nonrandomized and each patient had several risk factors for stent thrombosis, the incidence of stent thrombosis appeared to be ostensibly higher in CYP2C19*2 carriers than in non-carriers. Therefore, while this may not be the only cause of stent thrombosis, our data suggest that having a CYP2C19 polymorphism may be strongly associated with stent thrombosis through poor responsiveness to clopidogrel in the Japanese population, while we do not consider the CYP2C19 polymorphism alone to be a main cause of stent thrombosis.

Despite the incidence of the CYP2C19*2 polymorphism being markedly higher in the Japanese population than Western populations, the incidence of stent thrombosis among Japanese is reported to be rare as compared to Western patients [9,10]. We hypothesize the following two reasons for this discrepancy: First, IVUS is routinely used as an adequate and efficient procedure in many hospitals in Japan. Therefore, technical risk factors such as undersized stents, mal-apposition, and dissection may be largely avoided, and the influence of poor responsiveness to clopidogrel may be reduced by guarding against these technical factors. Second, the loading (300 mg) and the maintenance dosages (75 mg/day) of clopidogrel may be large for Japanese patients compared with Western patients, due to differences in body size. For intermediate metabolizers, the current dosage of clopidogrel may be sufficient to achieve an anti-platelet response. Several reports have suggested the need for weight-adjusted dosing of clopidogrel, as underdosing appears to be a primary predictor of failed dosing [11].

We previously demonstrated a significantly higher incidence of intra-stent thrombus in *2 carriers than in non-carriers (52.4% vs. 15.5%) using optical coherence tomography analysis six months after sirolimus-eluting stent implantation [12]. In this case intra-stent thrombus recognized in the third angiogram did not induce stent thrombosis. We therefore believe that patients with CYP2C19*2 polymorphisms have a high probability of developing subclinical intra-stent thrombi and are likely to have developed stent thrombosis in the presence of additional risk factors for stent thrombosis.

Finally, in this case, a platelet aggregation test showed good inhibition with 3 μg ADP and follow-up CAG showed disappearance of the stent thrombus after starting a new regimen of anti-platelet therapy (aspirin 100 mg + ticlopidine 200 mg + cilostazol 200 mg). Cilostazol reversibly inhibits platelet aggregation via its selective inhibition of phosphodiesterase type 3 and results in increased cyclic adenosine monophosphate in platelets [13]. This unique antithrombotic property inhibits phosphorylation of vasodilatator stimulated phosphoprotein, which is an active site of clopidogrel. Jeong et al. demonstrated that adjunctive cilostazol with normal-dose clopidogrel intensifies platelet inhibition as compared with a high maintenance dose of clopidogrel [14]. Therefore, we consider adjunctive cilostazol could be an alternative regimen to achieve an enhanced platelet inhibition in patients with clopidogrel resistance.

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