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Simultaneous subacute coronary artery stent thrombosis in a carrier of two CYP2C19 loss-of function polymorphisms (*2/*3)

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Clopidogrel, a second generation thienopyridine and a selective inhibitor of the platelet adenosine diphosphate (ADP) P2Y₁₂ receptor, is the historical standard anti-platelet treatment added to aspirin following percutaneous coronary intervention (PCI) in order to reduce the risk of stent thrombotic complications. Clopidogrel is an inactive pro-drug that requires hepatic metabolism by cytochrome P450 2C19 (CYP2C19) into its active form in order to inhibit platelet aggregation. Recently, substantial subpopulations have been recognized that exhibit an inadequate response to clopidogrel leading to insufficient antiplatelet effects [1]. Individuals carrying at least one loss-of function allele (either *2 or *3) of the CYP2C19 gene demonstrate reduced active clopidogrel metabolites and suppressed antiplatelet activity [2]. Such patients have been identified to carry a significantly higher risk of stent thrombosis, a major adverse event that is associated with >60% risk of death or myocardial [3]. Of note, the stent thrombosis risk in patients carrying a CYP2C19 loss-of function allele appears to be similarly elevated across stable and unstable patient populations, regardless of elective or urgent PCI, or treatment with bare metal or drug-eluting stents [4,5].

A 61-year-old dyslipidemic, non-diabetic male with stable angina presented for elective cardiac catheterization. Coronary angiography showed complex multivessel disease consisting of a proximal RCA chronic total occlusion (CTO) with collateral flow from conus branch of RCA and a diagonal branch (Fig. 1a, white arrow), and severe proximal LAD stenosis (Fig. 1d, white arrow). Based on the angiographic results, we first treated the RCA-CTO lesion by deploying three overlapping drug eluting stents (DES) (Promus Premier, Boston Scientific) with proximal to distal sizes of 3.5 × 24 mm, 3.0 × 24 mm and 2.5 × 28 mm. The mid stent and proximal stent were then post-dilated with 3.0 mm and 3.75 mm diameter non-compliant balloons, respectively. Post-PCI intravascular ultrasound (IVUS)

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Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

imaging confirmed good stent apposition with a sufficient stent/lumen diameter ratio in comparison to the proximal and distal reference vessel segments (Fig. 2, upper left panel). Four days later, staged PCI of the proximal LAD lesion was performed with implantation of a 3.0 × 23 mm DES (Xience Alpine, Abbott Vascular) with post-dilatation using a 3.0 mm diameter noncompliant balloon. Similar to the RCA results, good stent apposition was shown by IVUS (Fig. 2, upper right panel). Both procedures were successful with no complications (Fig. 1b and e, white arrows). The patient was continued uninterrupted on treatment with dual-antiplatelet therapy consisting of aspirin 100 mg and clopidogrel 75 mg daily, which had been started 30 days prior to the index PCI without adverse effects. He was discharged to home without angina and in stable condition.

The day following discharge, the patient developed sudden-onset severe chest pain and diaphoresis at rest. He presented within 2 hours of symptom onset in hemodynamically stable condition (blood pressure 157/92 mmHg, heart rate 83 beats per minute). The electrocardiogram revealed new ST elevations (>2 mm) with inverted T waves in V1 through V3, and stat echocardiography showed severe hypokinesis of the mid-distal-apical anterior wall. Blood tests returned with leukocytosis (12,500 cells/μl). Emergent coronary angiography for acute anterior ST elevation myocardial infarction (STEMI) was performed after administration of unfractionated heparin 5000 units, supported by an intra-aortic balloon pump (IABP), that showed thrombotic occlusion of both the RCA (Fig. 1c, black arrowhead) and LAD stents (Fig. 1f, black arrowhead). Given the clopidogrel failure, a loading dose of prasugrel (20 mg) was orally administered. GPIIb/IIIa inhibitor was not used. We then proceeded to restore flow in the LAD by passing a coronary guidewire through the stent and performing manual aspiration thrombectomy followed by subsequent percutaneous transluminal angioplasty (PTCA) with a 3.0 mm diameter balloon within the stent. Intracoronary optical coherence tomography demonstrated massive thrombus within the LAD stent despite excellent stent strut apposition throughout (Fig. 2, lower right panel). After achieving TIMI3 flow in the LAD (Fig. 1f, right bottom corner), we moved to treat the RCA with aspiration and PTCA in similar fashion resulting in return of TIMI3 flow in RCA (Fig. 1c, right bottom corner). Intracoronary OCT imaging in the RCA also showed massive thrombus in the distal stent (Fig. 2, lower left panel). The patient was discharged day 16 post-PCI on a medical regimen of an αβ-blocker (carvedilol, 5 mg once daily), an angiotensin converting enzyme inhibitor (Perindopril erbumine, 2 mg once daily) and dual anti-platelet therapy with prasugrel 3.75 mg and aspirin 100 mg once daily. At four months follow-up, the patient has been doing well without any evidence of recurrent myocardial ischemia. Genotyping of CYP2C19 gene polymorphisms revealed that the patient carries two reduced-function alleles (*2/*3) of the CYP2C19 gene, and he was thus defined as a poor clopidogrel metabolizer.

In this case, the patient carried two non-functioning polymorphisms (*2/*3) of the CYP2C19 gene, a deficit known to result in critically reduced clopidogrel antiplatelet activity, that precipitated simultaneous subacute stent thrombosis of two major epicardial coronary arteries. The frequency for the most common loss-of-function variant CYP2C19*2 is <15% in Caucasians and Africans, but affects up to 35% of those of Asian descent; in comparison, CYP2C19*3 is the second-most common genetic mutation, occurring in fewer than 10% of Asians [1]. Therefore, especially in Asian population, the number of patients

defined as a “poor clopidogrel metabolizer” carrying the CYP2C19*2/*2 or *2/*3 polymorphisms may be higher than previously postulated. To date, cardiovascular society guidelines recommend against routine gene testing for CYP2C19 polymorphisms for patients treated with clopidogrel after PCI [6,7], primarily because *a priori* knowledge of CYP2C19 genetic mutations or the results of platelet function testing have not demonstrated an improvement in outcomes [8]. However, while clinical trials may be equivocal, in certain high-risk individual patients, as presented in this case of an Asian patient undergoing elective complex PCI and suffering simultaneous subacute stent thrombosis, it might be reasonable to perform risk estimation using genetic screening or platelet reactivity testing before coronary stenting. In carriers of *2 and/or *3 alleles of CYP2C19 that have less or no CYP2C19 enzymatic activity (intermediate and poor metabolizers) on standard doses of clopidogrel (75 mg daily), two alternative strategies have been considered: 1) increasing the clopidogrel dose by two- to four-fold [9], which more potently decreases platelet activity but has not been proven to reduce cardiovascular events [10], or 2) the preferred approach of switching to alternative P2Y₁₂ inhibitors, such as the third generation thienopyridines prasugrel and ticagrelor that are less influenced by polymorphisms of the CYP2C19 gene. For prasugrel, carriers of the CYP2C19*2 allele are known to produce equivalent concentrations of active prasugrel metabolite and achieve a similar antiplatelet effect to those that do not carry this allele [5]. In this patient, clopidogrel was replaced by prasugrel with no clinical or adverse events observed in early follow up. Based on the clinical course of this case and related evidence, we suggest that when elective PCI is planned in certain patients at high risk for CYP2C19 polymorphisms, such as those of Asian descent, that are also at high risk for critical stent thrombosis due to complex multivessel or left main coronary artery disease, that physicians consider performing genetic testing for CYP2C19 polymorphisms or platelet function testing to evaluate the potential risk of using clopidogrel, or to simply use a third generation thienopyridine primarily.

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Fig. 1.

Coronary angiography at initial presentation for elective coronary stent placement, and following representation with ST elevation myocardial infarction due to subacute stent thrombosis. Before (a and d) and after (b and e) initial percutaneous coronary intervention (PCI) with drug-eluting stents, at simultaneous stent thrombosis (c and f), and after revascularization with aspiration thrombectomy and balloon angioplasty (figures at right bottom corner in c and f). White arrows indicate the target lesions where the initial PCI was performed, and black arrowheads indicate the lesions responsible for subacute stent thrombosis, respectively. RCA indicates right coronary artery, and LAD indicates left anterior descending artery.

Fig. 2. Intravascular ultrasound (IVUS) after initial PCI and intracoronary optical coherence tomography (OCT) imaging of multivessel stent thrombosis. Upper panels: IVUS demonstrated good stent expansion and apposition to the vessel wall. Lower panels: Massive stent thrombosis was observed by intravascular OCT (representative axial images and longviews). The homogenous, low backscattering OCT signal of the thrombotic material is consistent with a white (platelet-rich) thrombus. Scale bars indicate 1 mm.