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CASE REPORT

Subacute Stent Thrombosis in a Clopidogrel Resistant Octogenarian

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KEY WORDS: *coronary stent thrombosis, clopidogrel resistance, coronary angioplasty, optical coherence tomography*

Abbreviations
DES = drug eluting stent(s)
MI = myocardial infarction
OCT = optical coherence tomography
PCI = percutaneous coronary intervention

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ABSTRACT

An octogenarian on double clopidogrel maintenance dose (150 mg qd), due to clopidogrel resistance determined with a point-of-care assay, was subjected to percutaneous coronary intervention (PCI) of the left anterior descending coronary artery with two drug eluting stents. Twenty-four hours later the patient sustained subacute stent thrombosis manifesting as an anterior ST-elevation myocardial infarction with cardiogenic shock. Optical coherence tomography disclosed thrombus inside the stent without malapposition. Thrombus aspiration and balloon inflation of the thrombosed stent restored vessel patency. The issue of clopidogrel resistance and methods to overcome it are discussed.

INTRODUCTION

Subacute stent thrombosis with resultant abrupt vessel closure is one of the most common early complications of percutaneous coronary intervention (PCI), with dire consequences as it leads to high rate of Q-wave myocardial infarction (MI) and death. Subacute vessel occlusion was initially ascribed to increased stent thrombogenicity and inadequate antithrombotic therapy, and indeed since these regimens were optimized, the incidence of subacute stent thrombosis dropped to levels < 2%.[1] However, it still constitutes a major cause of death after PCI, despite the improvement noted in antiplatelet therapy, although the main cause nowadays appears to be suboptimal final results of stent implantation (e.g. stent under-deployment). This notwithstanding, resistance to antiplatelet therapy also seems to play an important role in this complication, [2-6] as will be shown in the present case.

CASE REPORT

An 83-year-old male was transferred from a district hospital to our tertiary center for primary angioplasty due to an acute lateral wall MI. Time from symptom onset was 3 hours and transfer time was 45 minutes. Aspirin (325 mg) and a clopidogrel loading dose (600 mg) were administered at the referring hospital, along with 5000 IU of unfractionated heparin. Coronary angiography from a right femoral approach disclosed total occlusion of the first marginal branch of the left circumflex artery (LCX), and

two 80-90% stenoses of the left anterior descending coronary artery (LAD) (Figure 1). A second bolus of unfractionated heparin (5000 IU) was administered at the catheterization laboratory. The total occlusion of the LCX was crossed with a guidewire and thrombus aspiration followed. After intravenous administration of standard abciximab loading, balloon angioplasty with a 2/15 mm balloon was performed and two overlapping paclitaxel drug eluting stents (DES) (Phoenix^{PicoTM}, Saudi Health Services Co. LTD, Jeddah, Saudi Arabia, 2.75/19 and 2.75/8 mm), were implanted successfully, followed by post-stenting inflation of a non-compliant balloon of the same size, restoring a TIMI-3 flow (Figure 1). The chest pain and ST-elevation resolved. The patient was transferred to the coronary care unit and had an uneventful course. Administration of aspirin 325 mg qd and clopidogrel 75 mg qd was continued for 24 hours, when in the context of a research protocol, post-clopidogrel platelet reactivity was measured with a point of care assay device (VerifyNow P2Y12 assay, Accumetrics Inc., San Diego, CA, USA). The latter was found to be 339 platelet reactivity units (PRU). With a cut-off value of 230 PRU for clopidogrel resistance the patient was considered resistant, and in the context of a research protocol following informed consent, he was randomized to a double clopidogrel maintenance dose (150 mg qd), in addition to aspirin 325 mg qd. The patient was also on statin, angiotensin converting enzyme inhibitor and beta-blocker therapy.

On the third post-MI day, the LAD lesions were treated successfully via a left femoral approach, with two paclitaxel DES (Infinium, Sahajanand Medical Technologies Pvt Ltd., Gujarat, India, 3/18 and 2.75/18 mm respectively), followed by post-stenting inflation of a non-compliant balloon of the same size (Figure 2). No further platelet glycoprotein IIb/IIIa inhibitor therapy was administered during the second PCI. On the next day the patient was transferred to the referring hospital. Twenty four hours following the LAD angioplasty, the patient sustained a new anterior acute MI with signs of acute pulmonary edema and was transferred back to our center for emergency coronary angiography. The latter was performed via a right femoral approach and disclosed thrombosis of the 2.75/18 mm DES with total occlusion of the LAD and thrombus extending up to the proximal DES (Figure 3). Thrombus aspiration was successfully performed and optical coherence tomography (OCT) imaging disclosed thrombus without malapposition of the two DES (Figure 4). Due to signs of cardiogenic shock with a blood pressure of 65/30 mmHg and patient confusion, an intra-aortic balloon was placed via the left femoral artery. Subsequently, balloon angioplasty with a 3/15 mm non-compliant balloon was performed in the two DES, with restoration of vessel patency and a TIMI-2 flow (Figure 3). The patient was initially stabilized and transferred to the coronary care unit. However, two days later the patient developed acute renal failure and signs of cardiogenic shock despite balloon counterpulsation and infusion of dobutamine

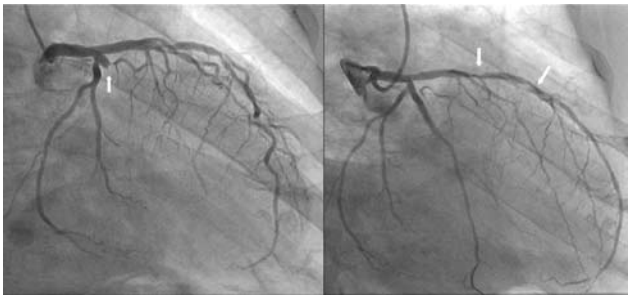

FIGURE 1. Coronary angiography during primary angioplasty. On the left, the totally occluded obtuse marginal branch is depicted (white arrow). On the right, vessel patency has been restored post-stenting with two overlapping DES (2.75/19, 2.75/8 mm). The two white arrows point to the LAD stenoses. LAD = left anterior descending artery, DES = drug eluting stent.

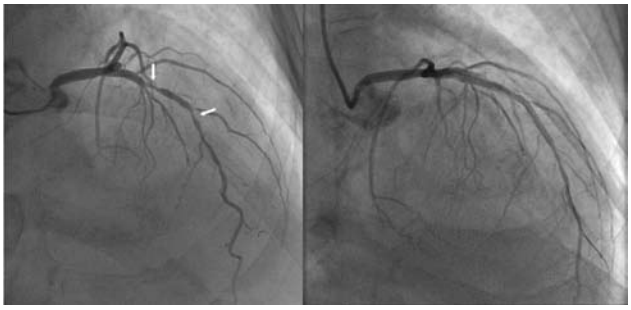

FIGURE 2. Coronary angiography during angioplasty of the LAD. On the left, the two white arrows point to the LAD stenoses. On the right, vessel patency has been restored post-stenting with two DES (2.75/18 mm for the distal lesion and 3/18 mm for the proximal lesion). LAD = left anterior descending artery, DES = drug eluting stent.

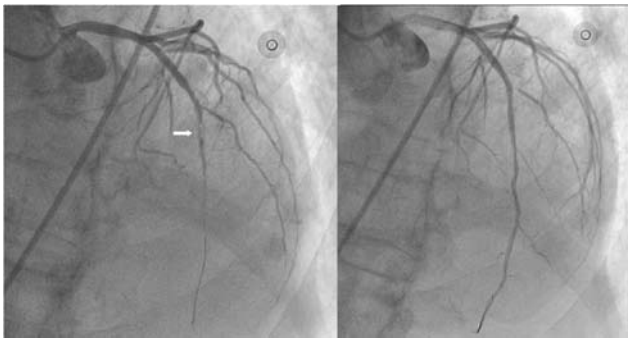

FIGURE 3. Coronary angiography. On the left, the white arrow points to the thrombosed LAD stent (2.75/18 mm). On the right, following thrombus aspiration and plain balloon angioplasty with a non-compliant 2.75/15 mm balloon, vessel patency has been restored. LAD = left anterior descending artery.

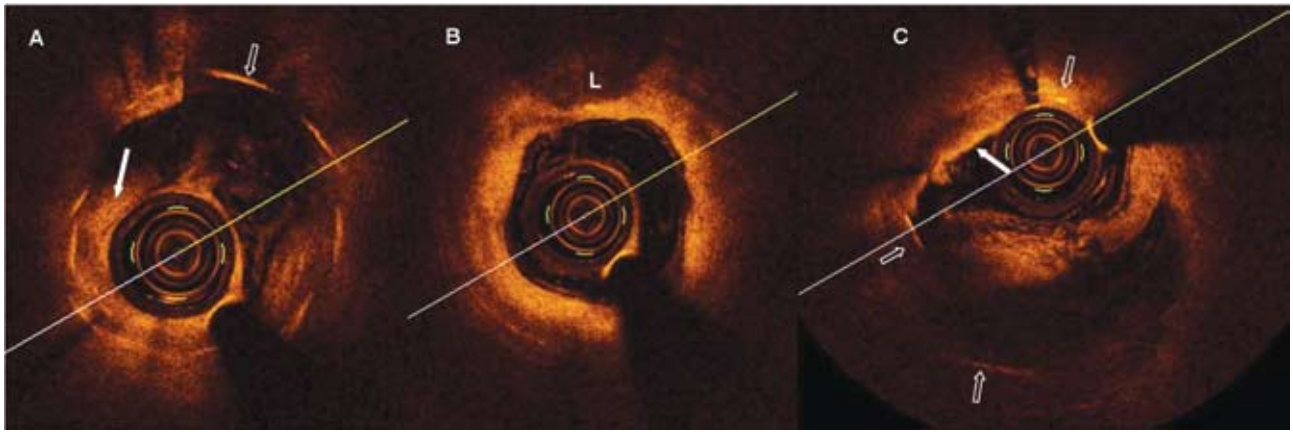

FIGURE 4. Three successive optical coherence tomography (OCT) images acquired following thrombus aspiration of the LAD. Panel-A acquired at the level of the thrombosed 2.75/18 mm DES, shows high-backscattering protrusions inside the lumen of the artery corresponding to red thrombus (closed white arrow). The open arrow points to a stent strut. Panel-B acquired between the 2 DES of the LAD, shows signal-rich concentric fibrous plaque with a lipid pool (L), at 12 o clock. Panel-C acquired at the level of the proximal LAD stent (3/18 mm), shows high-backscattering protrusions with signal-free shadowing corresponding to red thrombus (closed white arrow). The open arrows point to stent struts. LAD = left anterior descending artery, DES = drug eluting stent.

and dopamine, and eventually succumbed.

DISCUSSION

This case illustrates that subacute stent thrombosis may occur despite doubling of clopidogrel maintenance dose in patients considered to be clopidogrel resistant. On the other hand we should not underestimate the role of local conditions post-procedure (residual stenosis, dissection, non-optimal stent apposition, etc.) in providing the milieu for stent thrombosis.[1]

Clopidogrel resistance may be defined as clinical, i.e. ongoing thrombotic events despite clopidogrel therapy, or laboratory based on results of platelet function tests. The relative inhibition of platelet aggregation between pre-treatment and post-treatment is the most common estimate of clopidogrel responsiveness, however, patients responsive to clopidogrel may remain with highly reactive platelets and thus have increased thrombotic risk. It has been shown that assessment of clopidogrel responsiveness may be less clinically relevant compared to assessment of post-treatment platelet function as the latter is a better predictor of ischemic events.[2] Platelet function can be assessed ex-vivo with various methods, and the incidence of clopidogrel resistance reported lies between 5 and 44% depending on the population studied, the laboratory method used and the pre-specified cut-off values for defining clopidogrel resistance.[3-5] Although the reported incidence of clopidogrel resistance as determined with ex-vivo platelet reactivity assessment is high, the incidence of post-PCI clinical events is low (5-10%). This has raised concerns regarding the clinical relevance of such kind of assessment, however there is a lot of accumulating evidence that ex-vivo platelet function testing is associated with clinical events. [3,6-10]

Light transmitter aggregometry remains the gold standard for assessment of clopidogrel resistance, however it is neither widely available nor cost effective. Clopidogrel resistance determined with light transmittance aggregometry is associated with a high incidence of definite or probable stent thrombosis (up to 3 times higher compared to non-resistant patients), one year following PCI with DES.[11] Point-of-care assay devices (VerifyNow P2Y12 assay, Accumetrics Inc., San Diego, CA, USA) are now available and platelet reactivity is measured at the bedside in a few minutes. Platelet reactivity assessed with the latter is reported in platelet reactivity units (PRU), and post-treatment values above a certain limit define clopidogrel resistance. Obviously the higher the pre-specified cut-off value of PRU used for defining clopidogrel resistance, the less the incidence of the latter. High post-treatment platelet reactivity measured with a point-of-care platelet function assay was found to be associated with stent thrombosis post- PCI with DES.[12]

Various treatment strategies to reduce ischemic complications post-PCI and/or overcome clopidogrel resistance have been proposed, among which doubling the maintenance dose of clopidogrel (from 75 to 150 mg qd),[13] co-administration of IIb-IIIa inhibitors for resistant patients,[14] or switching to newer anti-platelet agents like prasugrel or ticagrelor. The CURRENT OASIS-7 study showed that doubling the loading dose of clopidogrel and administering a double maintenance dose (150 mg) for 7 days in patients with acute coronary syndromes undergoing planned PCI, significantly reduced stent throm-

bosis and cardiovascular events, largely driven by reductions in MI, without a significant increase in major bleeding.[15] We could speculate that this may in part be due to overcoming of the hypothetical clopidogrel resistance that might exist in some of the studied patients, by the higher dose. If this is correct, then screening for clopidogrel resistance in the catheterization laboratory, or post-PCI with a point-of-care device might be used routinely to recognize those patients that may benefit from a higher clopidogrel maintenance dose. However, our case exemplifies the fact that doubling the maintenance dose of clopidogrel in patients with clopidogrel resistance, may not be enough for reducing ischemic complications post-PCI with stenting. The 3T study showed that in aspirin, clopidogrel, or dual poor responder patients (detected with a point-of-care assay), with low-risk unstable coronary artery disease undergoing elective PCI, administration of tirofiban in addition to standard aspirin and clopidogrel therapy, lowers the incidence of post-PCI MI.[14] This concept needs further studying. Our patient had received abciximab during the primary PCI of the LCX, however a second administration of a IIb/IIIa inhibitor during PCI of the LAD was judged as potentially harmful by the interventionalist in an octogenarian being already on aspirin 325 mg and clopidogrel 150 mg qd.

Prasugrel, a potent and rapid-acting thienopyridine, is a potential alternative to clopidogrel. The recent TRITON-TIMI 38 study showed that in patients with ST-elevation MI undergoing PCI, prasugrel is more effective than standard clopidogrel for prevention of ischemic events, without an apparent excess in bleeding, apart from an increase in TIMI major bleeding after coronary bypass surgery.[16] In addition, the TRITON-TIMI 38 platelet sub-study demonstrated that prasugrel results in greater inhibition of ADP-mediated platelet function in patients with acute coronary syndrome than clopidogrel.[17] This finding also supports the hypothesis that greater platelet inhibition leads to a lower incidence of ischemic events with the cost of more bleeding both early and late following PCI. It is not known if the above results apply to the comparison between standard prasugrel treatment and double clopidogrel dose treatment, especially in patients resistant to standard clopidogrel treatment. Our patient was not switched to prasugrel treatment when clopidogrel resistance was diagnosed, as prasugrel is contra-indicated in octogenarians.

Apart from patient/physician non-compliance to clopidogrel treatment, real clopidogrel resistance is thought to be related to drug metabolism and biotransformation. Clopidogrel requires transformation into an active metabolite by cytochrome P-450 (CYP) enzymes for its antiplatelet effect. The genes encoding CYP enzymes are polymorphic, with common alleles conferring reduced function. In healthy subjects treated with clopidogrel, carriers of at least one CYP2C19 reduced-function allele had a relative reduction of 32.4% in plasma exposure to the active metabolite of clopidogrel, as compared with non-carriers, and an absolute reduction in maximal platelet aggregation in response to clopidogrel 9 percentage points less than that seen in noncarriers.[18] Among clopidogrel-treated subjects in TRITON-TIMI 38, carriers had a relative increase of 53% in the composite primary efficacy outcome of the risk of death from cardiovascular causes, MI, or stroke, compared with non-carriers and a 3-fold increase in the risk of stent thrombosis.[18] *Ticagrelor* is a novel oral, reversible, direct-acting inhibitor of the ADP receptor P2Y12, that has a more rapid onset and more pronounced platelet inhibition than clopidogrel. The recently published PLATO study showed that ticagrelor (180-mg loading dose, 90 mg bid thereafter), compared to standard clopidogrel treatment (300-to-600-mg loading dose, 75 mg daily thereafter), in patients with or without ST-segment elevation acute coronary syndromes, significantly reduced the rate of death from vascular causes, MI, or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding.[18] It may be that drugs like ticagrelor, which theoretically by-pass the principal mechanisms of clopidogrel resistance, will be the answer to this issue at least for some patients, however this remains to be proved.

LIMITATIONS

There are no guidelines regarding management of patients considered resistant to clopidogrel. Doubling of the clopidogrel maintenance dose in the above case, was done in the context of a research protocol and following patient's informed consent. This case exemplifies the fact that until randomized studies definitively show that a certain strategy or drug is recommended or preferred for such patients, cardiologists should be very cautious and more conservative and prudent regarding further management. The latter applies to our choice to proceed to LAD stenting very soon following the index procedure. Although this is the current practice in our center for all patients with multivessel disease following primary PCI, current guidelines advise otherwise, i.e. performing PCI of the culprit lesion only while postponing further revascularization for later on with staged elective procedures.[20-22] Only in the setting of cardiogenic shock there is consensus for attempting multivessel PCI.

The usage of two kinds of stents in the two procedures raises the issue of potential hypersensitivity reaction, which might have contributed to inflammation and thrombosis. However, there is no convincing evidence that this might have happened as systemic hypersensitivity symptoms and signs were absent in our patient, and the 2 DES used elute the same drug (paclitaxel). Alternatively, local hypersensitivity may be a tempting theory, but this has not been proved, and most reported hypersensitivity reactions to DES are either accompanied by systemic reactions, or happen late or very late post-stenting.[23-25] Usage of the same kind of DES with the same structure, polymer and eluted drug may be safer in

staged procedures; however this needs to be proved.

CONCLUSION

Laboratory clopidogrel resistance is associated with clinical resistance in some patients, with catastrophic consequences post-PCI with stenting. Doubling the standard clopidogrel maintenance dose of 75 mg in such patients may not be enough to overcome clinical resistance.

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