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Late Stent Thrombosis in a Patient of Clopidogrel Resistance: A Case Report

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ABSTRACT

Late stent thrombosis (LST) following drug-eluting stent (DES) implantation is a rare but very fatal complication after percutaneous coronary intervention (PCI). We report a case of LST presenting as non ST elevation myocardial infarction (NSTEMI) at 11 months after deployment of DES. The patient, initially managed with conventional dual-antiplatelet therapy (aspirin and clopidogrel) showed resistance to Clopidogrel on VerifyNow P2Y12 assay, and was subsequently substituted with prasugrel.

Key Words: Late stent thrombosis, Clopidogrel resistance, Prasugrel.

INTRODUCTION

Late Stent Thrombosis (LST), occurring between 1 month and 1 year following percutaneous coronary intervention(PCI), is a rare but fatal complication after drug-eluting stent (DES) implantation.[1-3] The dominant mechanism in LST appears to be delayed or incomplete re-endothelialization.[4-5] However, other factors that have been implicated include clopidogrel resistance, hypersensitivity to the stent polymer, drug interactions and premature discontinuation of antiplatelet agents. Clopidogrel resistance, which can be assayed by the VerifyNow P2Y12 test, appears to be a common phenomenon especially among South Asians owing to genetic polymorphisms in the Cytochrome P450 (CYP) enzymes,[6] and its association with LST has been reported. Newer generation thienopyridines such as prasugrel that provide significantly greater and more consistent inhibition of platelet aggregation may be used to reduce the risk of LST in susceptible individuals.[7] We report here a case of LST with demonstrated platelet resistance to clopidogrel, successfully substituted with prasugrel following re-stenting with DES.

Case Report:

A 71-year-old diabetic normotensive Bangladeshi gentleman, presented with the complaints of intermittent retrosternal chest tightness associated with sweating, occurring on exertion for a week and increasing over the preceding fifteen hours. He was a diagnosed case of ischaemic heart disease and had undergone PCI 11 months previously with implantation of DES. He had a history of myocardial infarction in 1990, following which he underwent Coronary Angiography (CAG) which revealed totally occluded Left Anterior Descending (LAD) artery with well-developed collaterals not requiring revascularization, and was started on coated Aspirin and Clopidogrel daily, in addition to a statin. Last year, following complaints of generalized weakness, he underwent an ETT, which was prematurely terminated due to shortness of breath. A subsequent CAG had shown totally occluded Left Circumflex (LCx) coronary artery in addition to LAD, and a DES was deployed in LCx. He was continued on dual antiplatelet therapy (i.e. aspirin and clopidogrel) since then.

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He presented this time with chest pain but in stable haemodynamic state. ECG revealed ST depressions in leads I, avL, V5-6, consistent with lateral ischaemia (Figure 1). Transthoracic echocardiography revealed apical and anterior wall hypokinesia and ejection fraction of 45-50%, Mild AR, grade II MR and DRA. Troponin I level was elevated at 3.02ng/ml (AMI diagnostic cut-off >0.6ng/ml); CK-MB was 40U/L (normal reference <25U/L). An emergency coronary angiogram revealed severe In Stent Restenosis (ISR) of 95-99% in the proximal-mid LCx with thrombus burden, and a 50% lesion in the distal LCx after origin of second obtuse marginal (OM2) vessel; OM2 had TIMI-I flow. LAD was totally occluded from its ostium and distally filled up retrogradely by RCA. [Figure 2(a)]. Urgent P2Y12 (VerifyNow™ Assay®, Accumetrics Inc., San Diego, CA, U.S.A.) was performed while the patient was on-table, to determine clopidogrel resistance. The VerifyNow P2Y12 assay revealed a P2Y12 Reaction Unit (PRU) of 314 (high on-treatment reactivity corresponding to clopidogrel resistance defined as PRU >208),[8] with a percentage inhibition of 7% (clopidogrel non-responsiveness defined as the percent inhibition of P2Y12 less than 20%).[9]

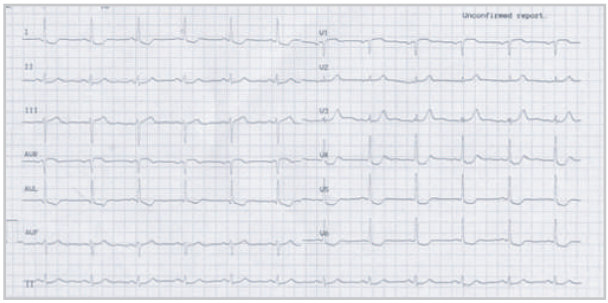

FIGURE 1 : *ECG showing ST depressions in leads I, avL, V5-6, consistent with a lateral ischaemia.*

As the P2Y12 assay was consistent with clopidogrel resistance, he was given a loading dose of prasugrel 60mg and proceeded to target vessel revascularization: using 6Fr XB 3.5 guide cath and BMW guidewire the LCx ISR lesion was crossed and sequentially predilated by a 2.0 x 10mm balloon at maximum 10ATM pressure. A 3.0x33mm DES stent was deployed at maximum 20ATM pressure for 20 seconds. Distal TIMI III flow was achieved without any immediate complication. [Figure 2(b)].

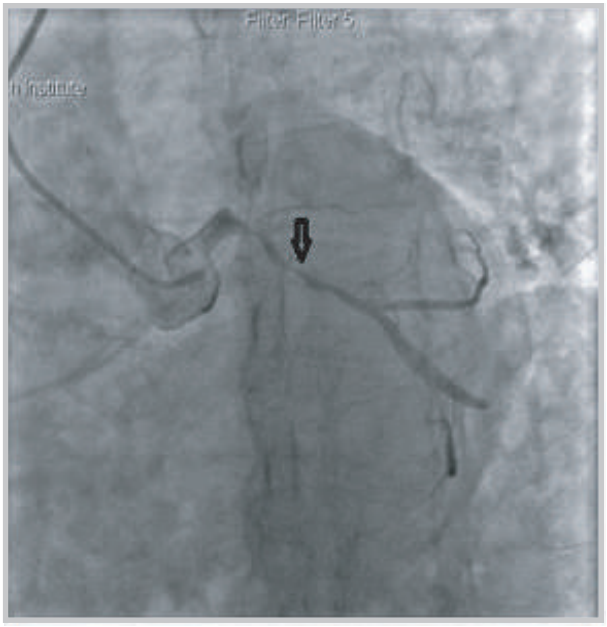

FIGURE 2(a) : *CAG showing severe ISR of 95- 99% in the proximal-mid LCx with thrombus burden and totally occluded LAD from its ostium.*

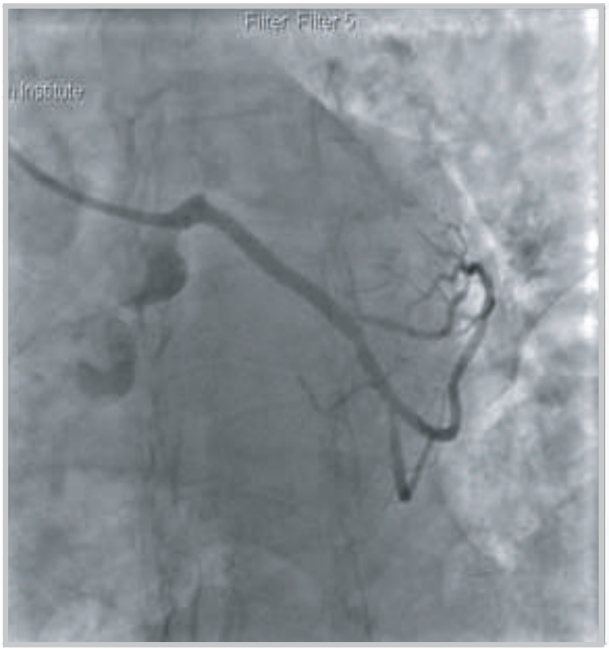

FIGURE 2(b) : *Distal TIMI III flow of LCx achieved following successful placement of a 3.0x33mm DES stent at the ISR lesion.*

CASE REPORT

The patient was discharged on dual anti-platelet regimen of aspirin and prasugrel after an uneventful recovery and gradual resolution of ECG changes (Figure 3), and has been asymptomatic at clinical follow-up.

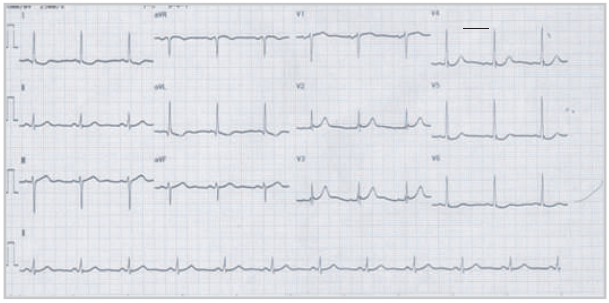

FIGURE 3: *ECG taken after stent deployment showing gradual resolution of ST depressions in leads I, avL, V5-6.*

DISCUSSION

With the widespread use of DES in recent times, there has been increasing concern that they may also be associated with an increased risk of LST, in comparison to Bare Metal Stents (BMS).[1-3] The Academic Research Consortium (ARC) consensus has classified Stent Thrombosis (ST) as definite, probable and possible; furthermore "definite" ST has been defined as angiographic or pathologic confirmation of partial or total thrombotic occlusion within the peri-stent region. Angiographic confirmation of ST requires the presence of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent plus at least one of the following criteria within a 48-hour time window: Acute onset of ischemic symptoms at rest; new ischemic ECG changes that suggest acute ischemia; or typical rise and fall in cardiac biomarkers.[10] The timing of ST has been further classified as acute (0 to 24 hours after stent implantation), subacute (> 24 hours to 30 days after stent implantation), late (>30 days to 1 year after stent implantation) and very late (> 1 year after stent implantation).[10]

Accordingly, our case, in which ISR occurred 11 months following PCI is categorized as LST. LST is a rare but fatal complication following DES implantation, resulting in MI in 60-70% of cases and mortality rates nearing 60%.[4,11] The dominant mechanism in LST appears to be delayed or incomplete re-endothelialization with DES.[4-5] Among other factors that have been implicated in the development of ST include Clopidogrel resistance, hypersensitivity to the stent polymer, drug interactions and the discontinuation of Clopidogrel within the first 6 months.[4,11]

The BASKET-LATE study,[3] which investigated the potential for LST owing to delayed arterial healing, demonstrated that the use of DES doubled the risk of LST and thrombosis-related events in comparison with BMS; also, in the year following discontinuation of Clopidogrel the rates of cardiac death or MI occurred more frequently with DES when compared to BMS(4.9 vs1.3%). In view of this, current recommendations advise that, following DES implantation, patients should receive clopidogrel (or an alternative thienopyridine) in addition to aspirin for a minimum of 12 months, unless contraindicated.[12] Premature discontinuation of antiplatelet therapy has been found to be the strongest predictor of LST.[11]

However, patients who continue to receive antiplatelet therapy but are non or poor responders to the effects of the agents also appear to be at increased risk of ST.[13-14] The more recent focus has been on varying individual response to clopidogrel, largely owing to genetic polymorphisms. Such a genetically acquired gene polymorphism manifests itself as clopidogrel resistance, measurable by platelet function tests, and is associated with adverse clinical events following PCI.[15]

Clopidogrel is a prodrug whose active metabolite effectively inhibits ADP-induced platelet activation and aggregation by selectively and irreversibly blocking the P2Y12 receptor.[14] The formation of the active metabolite of Clopidogrel is a two-step process performed by Cytochrome P450 (CYP450) enzymes, whose encoding genes appear to be polymorphic, with specific alleles (especially the low function CYP2C19*2, CYP2C9 and CYP2B6 alleles) being associated with decreased enzymatic activity and, consequently reduced

production of clopidogrel active metabolite. This leads to diminished platelet inhibition and higher rates of ST.[9, 16-17]

Clopidogrel resistance, more appropriately termed as clopidogrel 'non-responsiveness' is a phenomenon that may be defined as "the persistent activity of clopidogrel target (i.e. P2Y12 receptors of the platelet) despite an adequate antiplatelet regime".[9] Different mechanisms have been suggested; of which the most widely studied being the genetic polymorphisms of the CYP2C19 enzyme, whose frequency varies from 30% to 55% of the population depending on ethnic group and genetic background.[9] These genetic polymorphisms, found predominantly in patients such as ours originating from South Asia, are responsible for 99% of poor metabolizers.[6] Unfortunately, genetic testing, which would have provided valuable insight into racial polymorphism of the genes, could not be done due to lack of facilities.

Clopidogrel non-responsiveness is reported to vary between 4-44% among different populations.[9] In laboratory terms, clopidogrel resistance varies depending on the test used to quantify residual platelet reactivity. In our case, Clopidogrel low-responsiveness was assessed by the VerifyNow© P2Y12 assay, and defined as <20% inhibition of the P2Y12 receptor.[9] Alternatively, it may also be defined as high on-treatment platelet reactivity (HTPR) greater than 208 P2Y12 reaction units [PRU] by the VerifyNow test.[9] Our patient, with an on-treatment PRU of 314 and only 7% inhibition of platelet activity meets non-responder criteria to Clopidogrel, possibly responsible for the LST he had developed in LCx vessel.

Thus, if a patient develops ST while fully compliant with dual antiplatelet therapy, as in this case, consideration should be given to the modification of drug regimen.[18] Newer antiplatelet agents, including prasugrel[19] and ticagrelor, have been shown to be more potent, with a consequent reduction in ST, albeit at the risk of increased bleeding.[7] Given prasugrel's more rapid and greater pharmacodynamics,[20] and given that prasugrel demonstrates no genetic polymorphisms to CYP enzymes,[6] we chose to substitute clopidogrel for the new thienopyridine agent prasugrel in this patient.

ST among patients exhibiting clopidogrel resistance has been demonstrated in similar case reports[21,22] suggesting that, as in our case, platelet function testing following ST and also prior to administration of the loading dose of antiplatelet and subsequent stent deployment, may help physicians choose the optimal antiplatelet strategy; this may minimize the incidence of potentially fatal LST and recurrence of MI caused by ineffectiveness of standard therapy. However, pre-catheterisation testing of platelet function tests may not prove to be feasible routinely in our setting.

CONCLUSION

Given the increasing evidence of the incidence of genetic polymorphisms contributing to Clopidogrel resistance among South Asians, and the clear demonstration of prasugrel's clinical superiority, offset by increased bleeding risk in patients undergoing coronary artery stenting when compared to clopidogrel, it may also seems reasonable to offer antiplatelet coverage with prasugrel as opposed to clopidogrel in those showing no contraindications to the administration of the former.

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