Stent Thrombosis Revealing Resistance To Clopidogrel: A Case Report

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Abstract:
Drug-eluting stents (DES) are considered the treatment of choice for most patients with obstructive coronary artery disease when percutaneous intervention (PCI) is feasible. However, Stent thrombosis (ST) is a rare complication but have around 15-45% case fatality rate.

We report the cases of a young patient admitted for the management of a previous myocardial infarction related to subacute stent thrombosis.

The incidence of stent thrombosis is poorly understood around the world.
Several factors have been associated with ST, including patient specific factors (older age, black race and diabetes mellitus), procedure-related factors (stent underexpansion, incomplete apposition, greater stent length) and factors depending on the pharmacological therapy (non-compliance to anti-platelet agent and anti-platelet resistance).

Anti-platelet resistance is an independent predictor of ST, even several years after implantation of DES and increases the risk of ST.
Recent studies have shown that adequate anti-platelet effects are not achieved in 5% to 45% of the patients taking and in 4% to 30% of patients taking clopidogrel.

Currently, however, routine screening for antiplatelet resistance remains a persistent, unresolved issue and further evidence is necessary before it will be possible to recommend this testing as part of standard assessment of PCI candidates.

In addition, further prospective studies are needed to set guidelines for optimal treatment of patients with antiplatelet resistance who are at increased risk of ST, a catastrophic complication of DES implantation.

In the DES era, stent thrombosis is a fatal complication and antiplatelet therapy has been shown to be very important in preventing stent thrombosis. Thus, assessment of the patient's responsiveness to antiplatelet agents may be a crucial factor in monitoring these drugs' therapeutic efficiency and improving clinical outcomes after implantation of DES.

Keywords: stent thrombosis, clopidogrel, resistance.

Introduction
When Percutaneous Coronary Intervention (PCI) is feasible, Drug-Eluting Stents (DES) are the treatment of choice for most patients with obstructive coronary artery disease. Nonetheless, this therapeutic option has limitations which can lead to intra-stent restenosis and stent thrombosis which can be responsible for extremely serious myocardial infarction and sudden death.

However, Stent thrombosis is a rare complication with a 15-45% case fatality rate. Several factors are involved in the occurrence of this complication, including resistance to clopidogrel, which remains rare.

Keywords: stent thrombosis, clopidogrel, resistance.
Case report

A 59-year-old man smoker presented in the Department of Cardiology B, complaining of squeezing chest pain that had started the day before admission, associated with nausea. As cardiac risk factors, he presented diabetes mellitus type 2. He also reported a family history of coronary heart disease.

In physical examination, the patient was alert and cooperative. He was hemodynamically stable with no other abnormalities. The electrocardiogram showed normal sinus rhythm with a ST wave elevation in precordial leads with anterior myocardial infarction. The cardiac enzymes were elevated. The echocardiography showed akinesis of apical segments and severe hypokinesia of the anterior wall and middle segments of the septal wall, the left ventricular fraction of 35%.

The patient underwent coronary angiography that revealed a total thrombotic occlusion of the left coronary artery (LCA), and one drug-eluting stent were deployed in the LCA.

After the procedure, dual antiplatelet therapy (DAPT) with 75mg aspirin and 150 mg clopidogrel daily were given.

2 months after the procedure, the patient presented again another episode of chest pain. The electrocardiogram showed a ST elevation in the anterior leads with Q wave.

Emergent Coronary angiography revealed total thrombosis at the site of implantation of the stent deployed on the LCA. It was successfully treated with balloon angioplasty and a final angiogram revealed improved flow without intraluminal filling defect.

A VASP was requested and returned at 65%, indicating resistance to clopidogrel. For this, the patient was put on a double platelet antiaggregation based on Ticagrelor 90mg twice a day and aspirin 75 mg per day.

Our patient went onto a full and uneventful recovery after that and was discharge seven days later without any further complications.

No cardiac events were reported 15 days after his discharge, one month and three-month clinic follow-up.

Discussion

Stent thrombosis is a rare complication, but has a high case fatality rate of around 15-45%. (1) Academic Research Consortium (ARC) proposed a standard definition and classification of stent thrombosis which was derived from randomized trials (with a 4 year follow-up) including 878 patients treated with sirolimus stent, 1,400 with paclitaxel stent and 2,267 with bare-metal stent. (2) This definition included angiographically demonstrated thrombosis which occurs within hours of implantation (24h - acute thrombosis), during the first month (24h-30 days or subacute thrombosis), during the first year (late thrombosis) or beyond (> 1 year or very late thrombosis).

The incidence of stent thrombosis is poorly understood around the world. Early stent thrombosis in the first 24 hours after PCI still accounts for 6-25% of all stent thrombosis cases. The same rate for late stent thrombosis is between 0.8 and 5.8%. During the first year, this incidence is the same for bare-metal stents (BMS) and pharmacoactive stents.

Thus, in a single-center study conducted by de Man on 1309 patients treated with angioplasty, it was observed that 1.4% of patients with BMS stents presented with stent thrombosis and 1.9% of those who had pharmacoactive stent angioplasty have had this complication. (3)
Delay in re-endothelialization exposes the stent struts to bloodstream for a long duration and puts them at risk of stent thrombosis. The 2 types of stents are responsible for chronic inflammation, activation of platelet functions and the coagulation cascade which leads to the formation of the thrombus resulting in complete occlusion of the coronary artery. (4)

In the majority of cases, Stent thrombosis presents infarctoid chest pain associated with electrical changes localized to the area involved with previous PCI and elevated cardiac biomarkers. The mortality rate from myocardial infarction secondary to stent thrombosis can reach 45% despite emergency management, because acute thrombosis does not allow any preconditioning. (5)

Several factors have been associated with stent thrombosis, including patient specific factors (older age, black race and diabetes mellitus), procedure-related factors (stent underexpansion, incomplete apposition, greater stent length) and factors depending on the pharmacological therapy (non-compliance to anti-platelet agent and anti-platelet resistance). (6) The bifurcation lesion and the overlapped stents are also risk factors for stent thrombosis.

Clopidogrel resistance is an independent predictor of this thrombotic event in patients undergoing PCI. It has been reported to range between 16% and 50%. (7) Clopidogrel is a second-generation thienopyridine antiplatelet agent. It is a prodrug, one of the metabolites of which is an inhibitor of platelet aggregation. Clopidogrel must be metabolized by cytochrome P450 enzyme to synthesize its active metabolite which inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor P2Y12, and hence the activation of the GPIIbIIIa complex caused by ADP, so that platelet aggregation is inhibited. Following this irreversible fixation, the functioning of platelets is modified for the rest of their lifespan (approximately 7 to 10 days) and the restoration of normal platelet function corresponds to the period of platelet renewal. Platelet aggregation caused by other ADP agonists is also inhibited by neutralizing the amplification of platelet activation by released ADP. Because the active metabolite is synthesized by cytochrome P450 enzyme, some of which are polymorphic or inhibited by other drugs, not all patients will have adequate platelet inhibition.

Recent studies have shown that adequate anti-platelet effects are not achieved in 5% to 45% of the patients taking aspirin and in 4% to 30% of patients taking clopidogrel which suggests that many patients are resistant or only partially responsive to the antiplatelet agents. (8) If there is no response to clopidogrel, a response may be obtained with ticlopidine. However, this molecule is affected by the same variability of individual response.

Recently, the response to clopidogrel was evaluated by 2 methods: aggregometry with ADP which is the reference method whose use is still limited to specialized laboratories and requiring the need to strictly comply with several preanalytical methods such as sample processing time less than two hours after collection and platelet count adjustment and flow cytometric analysis of intraplatelet VASP method which is based on the measurement of the phosphorylation of the VASP protein by flow cytometry. This protein is involved in the inhibition of platelet activation. The latter technique allows a more specific evaluation of the response to clopidogrel. (9)

Many strategies for prevention of early stent thrombosis have been developed. Integer-based risk score may be applied to patient planned for PCI. This risk score may be used to identify patients who might benefit most from more aggressive antiplatelet therapy after stent implantation. (10) Without forgetting the verification of the various drug interactions with clopidogrel thus reducing its sensitivity, in particular with lipophilic statins which compete with clopidogrel at the level of cytochrome P450 or more recently with the omeprazole inhibitor. (5)
Currently, however, routine screening for antiplatelet resistance remains a persistent, unresolved issue and further evidence is necessary before it will be possible to recommend this testing as part of standard assessment of PCI candidates. In addition, further prospective studies are needed to set guidelines for optimal treatment of patients with antiplatelet resistance who are at increased risk of stent thrombosis, a devastating complication of DES implantation.

**Conclusion**

In the DES era, stent thrombosis is a fatal complication and anti-platelet therapy has been shown to be very important in preventing it. Thus, assessment of the patient's responsiveness to antiplatelet agents may be a crucial factor in monitoring these drugs' therapeutic efficiency and improving clinical outcomes after implantation of DES.

**References**