Case Report

Simultaneous double-culprit in-stent thrombosis. Who is the guilty prisoner behind bars: drug-eluting stent, bare-metal stent, or indication for treatment?

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Abstract

Background: The intrinsic thrombogeneity of stents was the historic limitation to their usage during the early phases of stenting. The risk of stent thrombosis has been minimized by the widespread use of platelet antiaggregation. Nowadays, the risk of subacute stent thrombosis is around 1%. Thrombotic risk depends on several factors, such as type of stent, complexity of lesion, and clinical picture.

Case Report: We present a case of recurrent acute in-stent thrombosis in a patient with mild antithrombin III (AT) deficiency despite the combined administration of clopidogrel and aspirin.

Conclusion: In our patient, several factors, such as diabetes, AT deficiency, and the use of a paclitaxel-eluting stent, have contributed to the development of recurrent acute stent thrombosis. Although we were not able to identify the culprit factor, we should keep in mind that the deployment of a drug-eluting stent could be unsafe if it is not supported by a clear clinically oriented pathway that considers the overall condition of the patient since, in some cases, neither coronary lesions nor coronary stents are responsible for the negative outcome of patient therapy, which may be caused instead by incomplete or inadequate patient assessment.

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Keywords: Acute stent thrombosis; Double platelets antiaggregation; Antithrombin III deficiency

1. Introduction

Stents are metallic coils that function as mechanical scaffolding and support for dilated lesions and that have been proven to reduce the incidence of restenosis [1–3]. These devices, however, are made of metal and can further activate the already present prothrombotic state brought about by underlying endothelial damage and diseases. Acute stent thrombosis (AST) and subacute stent thrombosis (SAST), defined as angiographically confirmed in-stent thromboses occurring within 24 h or up to approximately 30 days, respectively, following percutaneous coronary interventions (PCIs) are feared complications that may follow a successful PCI in the hours or days immediately following it.

In the previous year, the incidence of AST and SAST declined; nowadays, it is on the order of, or even lower than, 1% [4–8]. These data have been recently confirmed with the use of newer paclitaxel-eluting stents (PES) [9]. This

Abbreviations: LAD, left anterior descending; RCA, right coronary artery; IVUS, intravascular ultrasound; PES, paclitaxel-eluting stents; AST, acute stent thrombosis; SAST, subacute stent thrombosis; AT, antithrombin III.

The final text has been approved by all authors. No conflict of interest exists.

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relatively low incidence of this much dreaded complication has been achieved with the widespread usage of the combination of aspirin and thienopyridines (clopidogrel or ticlopidine) in the periprocedural period and in the months following a stent procedure. With the number of percutaneous stent procedures increasing worldwide, the absolute number of patients who incur in-stent thrombosis is not negligible [10,11].

Stent thrombosis is a much dreaded complication, with 20–25% mortality in the short-term phase of the event and with a 60% risk of nonfatal myocardial infarction [5,7]. With such gloomy outcome, it becomes increasingly important to understand the pathophysiology of stent thrombosis to try to prevent it. The main factors involved in stent thrombosis are classified into four categories: factors involving the stent (material, polymer, cell design, and strut thickness) [5,12,13]; factors involving the patient (primary stenting for acute myocardial infarction, diabetes mellitus, left ventricular dysfunction, and hypersensitivity to the polymer or to the metal) [14]; factors involving the lesion being treated (small vessel and long lesions) [15]; and factors involving the procedural technique (hypoexpansion of stent struts, malapposition, residual dissection, and multiple stenting) [12,16].

2. Case report

The patient is a 57-year-old White male who is a heavy smoker with a past medical history that is significant for noninsulin-dependent diabetes mellitus and hypertension. Pertinent results included negative findings for coronary artery disease. The patient, presenting with an anterior ST elevation myocardial infarction (STEMI) complicated by pulmonary edema, was emergently admitted to another institution without an on-site catheterization laboratory. The patient was initially treated with thrombolytic therapy. Due to the persistence of the symptoms, the patient was transferred to another institution where a coronary angiogram showed severe triple-vessel disease with a severe eccentric ulcerated plaque of the left anterior descending (LAD) artery and subocclusion of the proximal left circumflex artery and the medial right coronary artery (RCA).

The LAD artery was successfully treated with rescue angioplasty and stenting (3.0×15 mm at 11 atm, TECNIC; Sorin) and with Thrombolysis in Myocardial Ischemia...
(TIMI) III flow at the end of the procedure. The patient was then admitted to the coronary care unit while on treatment with clopidogrel (75 mg, po, qd) and aspirin (300 mg, po, qd), and was subsequently transferred to the telemetry unit. While on telemetry 96 h postprocedure, the patient developed a new episode of pulmonary edema complicated by ventricular fibrillation, which was successfully terminated by electrical defibrillation at 200 J.

A new coronary angiogram showed an acute total occlusion of the LAD stent, which was successfully reopened with balloon angioplasty. The patient was then referred for rehabilitation medicine. On the 17th day after myocardial infarction, he developed a new episode of pulmonary edema and was again transferred emergently to the catheterization laboratory, where a new coronary angiography showed a new SAST with a complete occlusion that was successfully treated.

Fig. 3. ECG shows ST elevation on inferior and anterior leads.

Fig. 4. Simultaneous AST of the LAD artery and the RCA.
with balloon angioplasty (3.0×20 mm at 13 atm, MAVERICK; Boston Scientific) with restoration of TIMI III flow. The patient was again admitted to the coronary care unit with intra-aortic balloon counterpulsation, inotropes, and endotracheal intubation.

Once weaned off the abovementioned support, the patient was transferred to our tertiary center for evaluation in a dedicated heart failure facility as a possible candidate for heart transplant.

We decided to proceed with a new coronary angiography, which showed patency of the LAD stent and confirmed the subocclusion of the proximal left circumflex artery and the medial RCA (Fig. 1). Intravascular ultrasound (IVUS) of the LAD artery showed good stent apposition throughout.

We then proceeded to revascularize the RCA, which we successfully achieved with balloon dilatation (2.0×20 mm at 10 atm; JoMed) and two PES (3.0×28 mm at 16 atm and 3.0×20 mm at 16 atm, TAXUS; Boston Scientific), with good angiographic results and TIMI III flow. The procedure was performed with unfractionated heparin (100 IU/kg; activated clotting time, 230–250 s) followed by eptifibatide infusion for 18 h (Fig. 2).

The patient was then admitted to our coronary care unit where, 12 h later, he started complaining of chest pains, quickly became hypotensive, and went into frank cardiogenic shock.

An electrocardiogram (ECG) performed at this time showed ST elevation inferiorly and anteriorly (Fig. 3). The patient was emergently brought to the catheterization laboratory where intra-aortic balloon counterpulsation was performed and where coronary angiography showed occlusion of both LAD and RCA stents (Fig. 4). The patient was successfully treated with a new angioplasty of the LAD artery [balloon predilatation (3.0×20 mm at 12 atm, MAESTRO; JoMed) and IVUS (no evidence of dissection; stent underexpansion with a 4.0-mm referral vessel diameter) followed by dilatation of a new balloon (3.5×15 mm at 12 atm, MAVERICK; Boston Scientific] and stent deployment (4.0×18 mm at 12 atm, DRIVER). Then we treated the RCA in-stent acute thrombosis by balloon angioplasty (3.0×15 mm at 14 atm, MAESTRO; JoMed) with restoration of TIMI III flow (Fig. 5).

The IVUS performed at the end of the procedure did not show dissection, and the stent was correctly apposed. In the

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Results</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets (mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>264,000</td>
<td>180,000–300,000</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time [s (‰)]</td>
<td>13.63 (76.04)</td>
<td>10–15 (80–120)</td>
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<td>INR</td>
<td>1.19</td>
<td>0.8–1.2</td>
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<td>Activated partial thromboplastin time (s)</td>
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<td>25–35</td>
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<tr>
<td>Fibrinogen (mg/dl)</td>
<td>327</td>
<td>250–470</td>
</tr>
<tr>
<td>AT activity (%)</td>
<td>66</td>
<td>80–100</td>
</tr>
<tr>
<td>Protein C (%)</td>
<td>111</td>
<td>69–134</td>
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<tr>
<td>Protein S (%)</td>
<td>123</td>
<td>57.6–112.5</td>
</tr>
<tr>
<td>Omocisteina (μmol/l)</td>
<td>6.98</td>
<td>5.90–16</td>
</tr>
</tbody>
</table>

The patient was successfully treated with a new angioplasty of the LAD artery [balloon predilatation (3.0×20 mm at 12 atm, MAESTRO; JoMed) and IVUS (no evidence of dissection; stent underexpansion with a 4.0-mm referral vessel diameter) followed by dilatation of a new balloon (3.5×15 mm at 12 atm, MAVERICK; Boston Scientific] and stent deployment (4.0×18 mm at 12 atm, DRIVER). Then we treated the RCA in-stent acute thrombosis by balloon angioplasty (3.0×15 mm at 14 atm, MAESTRO; JoMed) with restoration of TIMI III flow (Fig. 5).
following days, the patient maintained clinical stability, and a follow-up echocardiogram performed a week later showed an ejection fraction of 30%. The patient was hemodynamically stable and was classified as New York Heart Association Class II upon discharge. A complete hypercoagulable state workup was pursued, and antithrombin III (AT) activity was 66%, which was slightly below normal limits (Table 1). The patient was discharged on aspirin (100 mg, po, qd), clopidogrel (75 mg, po, qd), and warfarin to keep the international normalized ratio (INR) between 2 and 3, and he has been clinically stable since. A follow-up coronary angiography at 2 months confirmed the patency of the LAD and RCA stents (Fig. 6).

3. Discussion

SAST occurs in 0.8% of patients with coronary bare-metal stents [8]. It is related to some mechanical risk factors, such as stent underexpansion or malapposition and low flow state. In 2003, Farb et al. [17] described 13 cases of late stent thrombosis (LST) with impaired intimal healing, demonstrating the importance of unpredictable coronary endothelial dysfunction. DES implantation is a risky procedure that may irreversibly jeopardize the coronary endothelium. PES or sirolimus-eluting stents can intrinsically compromise endothelial function, and caution must be suggested in overlapping, as differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus-eluting stents or PES have been shown [18]. In most cases, this persistent inflammation leads to LST; however, we cannot exclude that, in our patient, it might have contributed to the acute event, in addition to other predisposing factors.

A recent study concludes that the cumulative incidence of stent thrombosis 9 months after the successful implantation of drug-eluting stents (DES) in consecutive “real-world” patients is substantially higher than the rate reported in clinical trials. Premature antiplatelet therapy discontinuation, renal failure, bifurcation lesions, diabetes, and low ejection fraction were identified as predictors of thrombotic events [19].

This unusual case of double simultaneous stent thrombosis deals with important clinical implications. The patient was previously treated by LAD bare-metal stent, complicated by several episodes of SAST. In such peculiar clinical context, the use of DES should have been probably avoided. Although a moderate decrease of anti-thrombin III (AT) levels was subsequently discovered during a broad coagulation assessment workup, not all intrastent thromboses can be associated with the state of AT deficiency. The question is whether a patient with an altered thrombosis condition may be treated more effectively with a direct thrombin inhibitor instead of a glycoprotein IIb–IIIa inhibitor. The issue remains open.

IVUS examination showed perfect apposition and expansion of the stents implanted on the RCA. Thus, no mechanical dysfunction of coronary prosthesis can be advocated as responsible for subacute thrombosis. However, two PES were overlapped to obtain good epicardial coronary flow improvement. Such overlapping should probably have been avoided, preferring the use of a single long stent. The simultaneous occlusion of double-culprit stent-treated lesions is a rather unusual complication of PCI, even though it may happen due to the inherent hemodynamic compromise caused by the initial occlusion of the first stent.

More than specific culprit lesions, the long history of this patient seems to demonstrate that at least several
different culprit factors, such as moderate antithrombin deficiency, endothelium dysfunction, and use of DES, influenced the complicated outcome of this patient. Culprit is the proper term for a guilty prisoner behind bars. The word is a combination of two Anglo-French legal words, culpable and guilty, and prit or prist (i.e., prest) is an Old-French word for “ready.” As for culprit lesions, one should bear in mind that lesions are sometimes not the cause of—but an indication for—treatment. We must be very cautious when placing DES. Their use should always be supported by a clear clinically oriented pathway that considers the overall condition of the patient since, in some cases, neither coronary lesions nor coronary stents are responsible for the negative outcome of patient therapy, which may instead be caused by incomplete or inadequate patient assessment.

4. Conclusions

1. Patients with repeated episodes of SAST should be carefully assessed for coagulability status.
2. Patients with moderate levels of AT might benefit from bivalirudin protection during coronary stenting.
3. DES should be avoided in patients with previous subacute stent thrombosis or LST.

References