Intravascular Ultrasound and Histology Findings in Very Late Bare-Metal Stent Thrombosis

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INTRODUCTION

Very late stent thrombosis in an implanted bare-metal stent is a very uncommon event outside the context of brachytherapy and few data about its pathophysiology are available. We performed an intravascular ultrasound study during primary angioplasty in five patients with very late bare-metal stent thrombosis and carried out a histological analysis of the material removed by manual thrombectomy. The mean time from the index procedure was 7 (4) years. Intravascular ultrasound findings were: calcified atherosclerosis with in-stent plaque rupture, complex plaque in the distal segment of the stent, in-stent neointimal proliferation associated with underexpansion, and severe in-stent proliferation. Histological findings were consistent with the intravascular ultrasound images: recent thrombus with areas of old thrombosis in all cases and remnant atheromatous plaque and endothelium. Consequently, in-stent or distal stent atherosclerosis progression and progressive neointimal proliferation were the likely pathophysiological mechanisms.

Key words: Stent. Thrombosis. Restenosis. Myocardial infarction. Ultrasound.

METHODS

We studied 5 patients with an acute coronary syndrome acute coronary syndrome and ST segment

Hallazgos de ecografía intravascular e histológicos de trombosis muy tardías de stents convencionales

La trombosis muy tardía tras el implante de un stent convencional es un evento muy infrecuente fuera del contexto de la braquiterapia y apenas existen datos sobre su fisiopatología. Estudiamos a 5 pacientes con trombosis muy tardía tras stent convencional a quienes se realizó ecografía intravascular durante el intervencionismo primario y análisis histológico del material extraído tras trombectomía manual. La media de tiempo desde el implante fue 7 ± 4 años. Los hallazgos ecográficos fueron: aterosclerosis calcificada con placa rota intra-stent, placa compleja en el borde distal del stent, proliferación neointimal intra-stent en relación con infraexpansión y proliferación severa intra-stent. La histología fue concordante con la imagen intravascular: trombo reciente con zonas de trombosis antigua en todos los casos y restos de placa de ateroma y endotelio. Por lo tanto, la progresión de la aterosclerosis intra-stent o en bordes y la progresión de la proliferación neointimal fueron los factores fisiopatológicos plausibles.

elevation secondary to VLST of a BMS. All of them underwent an emergency primary percutaneous coronary intervention. Once the angioplasty guidewire had passed through the thrombotic lesion, manual thrombectomy was performed using the Export device (Medtronic). In 1 case, the catheter did not pass through the lesion and balloon dilatation was performed. An IVUS study was carried out after thrombectomy in 4 patients and following balloon dilatation in 1. We used the IVUS findings to guide the interventional procedure, which ended with implantation of a stent-in-stent in 4 patients and dilatation with a noncompliant balloon alone in 1. Abciximab was administered in every case and the outcome was satisfactory, with Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow and optimal myocardial perfusion.

For the histological study, the samples were fixed in 4% formaldehyde for at least 7 days and embedded in paraffin; 4.3-µm sections were obtained and stained with hematoxylin and eosin. Recent thrombus was defined as that composed of platelets and polymorphonuclear cells agglutinated by fibrin and mixed with the red blood cells. Recent thrombus was defined as that composed of platelets and polymorphonuclear cells agglutinated by fibrin and mixed with the red blood cells. Recent thrombus was defined as that composed of platelets and polymorphonuclear cells agglutinated by fibrin and mixed with the red blood cells. Recent thrombus was defined as that composed of platelets and polymorphonuclear cells agglutinated by fibrin and mixed with the red blood cells. Recent thrombus was defined as that composed of platelets and polymorphonuclear cells agglutinated by fibrin and mixed with the red blood cells.

### RESULTS

Table 1 shows the clinical, intravascular, and histological findings in each patient. All were men, with a mean age of 69 (11) years, and were receiving indefinite antiplatelet therapy. The lesion was located in the mid-segment of left anterior descending artery in 5 patients, the proximal segment of the first diagonal branch in another 2 and in the middle segment of left anterior descending artery in the fifth. The mean time elapsed between the initial procedure and the thrombotic event was 7 (4) years. The angiographic finding was complete stent occlusion in all the patients. The IVUS revealed: de novo atherosclerosis with severe circumferential and surface calcification at the level of the stent, with ulcer and remains of the fibrous capsule indicative of plaque rupture (Figure 1) and a complex plaque with an intraluminal thrombus on the distal edge of the stent, with moderate stent proliferation (Figure 2). In another patient, we observed underexpansion of the stent with mild proliferation and, finally, in the other 2 patients, a severe neointimal proliferation predominated (Figure 3).

The histological findings were concordant with those of IVUS. In every case, there was a recent thrombus; in 2 cases, an old thrombus predominated; in 1 case, the remains of an atheromatous plaque were removed; and, in another case, we found the remains of neointimal proliferation.

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**TABLE 1. Clinical Angiographic and Histological Characteristics of the Patients With Very Late Bare-Metal Stent Thrombosis**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Sex</th>
<th>Vessel</th>
<th>Time to ST, mo</th>
<th>Angiographic Findings</th>
<th>ICU Findings</th>
<th>Weight Aspirated</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>64</td>
<td>M</td>
<td>RC</td>
<td>90</td>
<td>Complete in-stent occlusion of middle RC segment</td>
<td>Calcified atherosclerosis and ruptured in-stent plaque with image indicative of thrombus</td>
<td>9 mg</td>
<td>Fragments of recent thrombus, calcium and remains of atheromatous plaque</td>
</tr>
<tr>
<td>75</td>
<td>M</td>
<td>RC</td>
<td>120</td>
<td>Complete in-stent occlusion of middle RC segment</td>
<td>Ruptured complex plaque on distal stent edge with positive remodeling and image indicative of thrombus. In-stent neointimal proliferation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>78</td>
<td>M</td>
<td>Diagonal</td>
<td>15</td>
<td>Complete in-stent occlusion of proximal diagonal segment</td>
<td>Mild neointimal proliferation. Underexpansion with image indicative of thrombus.</td>
<td>8.7 mg</td>
<td>Predominance of recent thrombus component</td>
</tr>
<tr>
<td>76</td>
<td>M</td>
<td>Diagonal</td>
<td>63</td>
<td>Complete in-stent occlusion of proximal diagonal segment</td>
<td>Severe neointimal proliferation and underexpansion. Image indicative of thrombus</td>
<td>32 mg</td>
<td>Predominance of old thrombus and presence of neointima</td>
</tr>
<tr>
<td>54</td>
<td>M</td>
<td>ADA</td>
<td>110</td>
<td>Complete in-stent occlusion of middle ADA segment</td>
<td>Severe neointimal proliferation. In-stent atherosclerosis and image indicative of thrombus</td>
<td>17 mg</td>
<td>Predominance of old thrombus</td>
</tr>
</tbody>
</table>

ADA indicates anterior descending artery; ICU, intracoronary ultrasound; M, man; RC, right coronary artery; ST, stent thrombosis.
DISCUSSION

The 2 pathophysiological mechanisms of VLST in a BMS suggested in this study are the development and progression of de novo atherosclerosis within the stent or on its edges, as well as in-stent neointimal proliferation. These factors differ from the mechanisms involved in late or very late DES thrombosis. The major local mechanism associated with VLST in DES are incomplete and delayed endothelialization of the stent, alone or in combination with chronic inflammation and a hypersensitivity reaction that results in positive arterial remodeling and incomplete apposition.5,6 Other factors reported for VLST in DES are underexpansion and penetration of the stent into the necrotic core, mainly in patients with acute coronary syndrome.5,6

Very late stent thrombosis is a rare complication in BMS and very few cases have been reported.3,7-12 Table 2 shows the 8 cases that we have found
its possible fracture and the subsequent thrombus formation.

The other mechanism that we describe is the progression of atherosclerosis within the in-stent neointima or on the edges. In the literature, we have found no description of plaque rupture due to IVUS within the neointima, although there is 1 case with angiographic and histological documentation using material collected by means of thrombectomy. Our series includes a case with plaque rupture in the context of de novo atherosclerosis within the in-stent neointima and another case of atherosclerotic plaque rupture on the distal edge of the stent. The formation and progression of atherosclerosis in the
in-stent neointima probably requires the passage of several years. In the cases in our series in which there was complicated atherosclerosis within the stent or on its edges, 90, 110, and 120 months had elapsed. In contrast, in those cases in which neointimal proliferation is identified as the major mechanical mechanism, the time to the event was much shorter (15 and 63 months).

All of the patients in our series were being treated indefinitely with an antiplatelet agent and had dual antiplatelet therapy during the first month after implantation. In contrast to the case of DES, it is not clear whether the indefinite prolongation of dual antiplatelet therapy is capable of preventing VLST in BMS.

Finally, it is important to perform an intracoronary imaging technique such as IVUS to obtain information on the mechanism of the thrombosis, with a view to percutaneous treatment during the event. Thus, when there is atherosclerosis within the stent or on the edges and severe restenosis, the implantation of another stent makes it possible to obtain an optimal result. If what predominates is the thrombus with mild restenosis, related or not to underexpansion, the outcome can be optimized by means of balloon dilatation without implantation of a new stent.

To conclude, the findings of this study indicate that the pathophysiology of VLST in BMS may differ from that associated with DES. The progression of atherosclerosis within the stent or on the edges and neointimal proliferation are the major factors in the development of VLST in BMS.

REFERENCES


