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

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.


INTRODUCTION

Very late stent thrombosis (VLST), that which occurs more than a year after implantation, has recently been described and studied because of the growing use of first generation drug-eluting stents (DES). The incidence usually ranges between 0.4% and 0.6% per year, and the major mechanism involved in the pathophysiology of VLST of a DES is incomplete endothelialization.1,2 Very late stent thrombosis of bare-metal stents (BMS) is a very uncommon complication outside the context of brachytherapy and the underlying pathophysiological mechanisms are little known.3 Our objective is to provide an in-depth evaluation of the pathophysiological knowledge of this complication by describing the intravascular findings revealed by intravascular ultrasound (IVUS) and its histological correlation of the samples collected after manual thrombectomy in 5 patients with definitive thrombosis after implantation of a BMS. Likewise, we provide a brief review of the literature dealing with the IVUS findings related to VLST following implantation of a BMS.

METHODS

We studied 5 patients with an acute coronary syndrome acute coronary syndrome and ST segment...
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 right coronary artery in 2 cases, in 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 in-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).

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. In the most highly developed thrombus, we observed a more compact agglutination of the polymorphonuclear cells, in which the nuclei are fragmentated and the platelets replaced by fibrin. A fragment of an atherosclerotic plaque was defined as the part of the necrotic core with calcium and the presence of macrophages with lipids in the cytoplasm.

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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.
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 atheroclerosis 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

Figure 3. Corresponds to patient no. 4 in Table 2. A: angiogram showing complete occlusion in proximal segment of first diagonal branch. B: intracoronary ultrasound image with longitudinal reconstruction and transverse sections. The transverse sections show severe neointimal proliferation with distal underexpansion of the stent. C: fragments of old thrombus with lysis of the nuclei of the polymorphonuclear cells and surface endothelialization (H-E, ×200). At greater magnification, we see endothelial cells of the in-stent neointima (H-E, ×400).

### TABLE 2. Publications to Date With Description of the Intravascular Findings

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases</th>
<th>Delay, mo</th>
<th>Findings in Intravascular Ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayashi et al.⁷</td>
<td>2</td>
<td>27 and 31</td>
<td>Stent malapposition in both cases. No atherosclerotic plaque dissection or rupture</td>
</tr>
<tr>
<td>Ishikawa et al.⁸</td>
<td>1</td>
<td>19</td>
<td>Mild neointimal proliferation. No atherosclerotic plaque dissection or rupture</td>
</tr>
<tr>
<td>Celik et al.⁹</td>
<td>1</td>
<td>16</td>
<td>Incomplete stent expansion. No atherosclerotic dissection or rupture</td>
</tr>
<tr>
<td>Saito et al.¹⁰</td>
<td>1</td>
<td>29</td>
<td>Mild neointimal proliferation. No atherosclerotic plaque dissection or rupture</td>
</tr>
<tr>
<td>Lemesle et al.³</td>
<td>1</td>
<td>96</td>
<td>Mild neointimal proliferation. No atherosclerotic plaque dissection or rupture</td>
</tr>
<tr>
<td>Trabattoni et al.¹¹</td>
<td>1</td>
<td>14</td>
<td>Severe neointimal proliferation</td>
</tr>
<tr>
<td>Ponnuthurai et al.¹²</td>
<td>1</td>
<td>60</td>
<td>Neointimal proliferation in proximal segment and image compatible with thrombus in distal segment of saphenous vein graft</td>
</tr>
</tbody>
</table>
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


