Early restenosis after drug-eluting stent implantation: A putative role for platelet activation

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Drug-eluting stents (DES) reduce intimal hyperplasia and restenosis, but they also inhibit stent endothelialization, making the vascular surface more thrombogenic. The present report describes two cases of in-stent restenosis after DES deployment at exactly the same sites where subacute stent thrombosis had occurred. Extremely careful follow-up is mandatory after the recognition of intraluminal thrombi inside DES because restenosis may occur at the same site of DES thrombosis.

Key Words: Angioplasty; Restenosis; Stents; Thrombus

Drug-eluting stents (DES) are coated with antiproliferative agents that reduce neointimal formation (1) and substantially reduce restenosis compared with bare metal stents (2,3). However, the eluted drug inhibits stent endothelialization, potentially rendering the inner stent surface more thrombogenic, and raises concern about a higher risk of stent thrombosis (4).

In the present report, the occurrence of in-stent restenosis is documented in two patients after DES deployment at exactly the same sites where subacute stent thrombosis had occurred.

CASE PRESENTATIONS

Case 1

A 65-year-old man was admitted for effort angina three years after bypass surgery with the left internal mammary artery to the left anterior descending coronary artery (LAD), as well as a single saphenous vein graft sequentially anastomosed to the first diagonal, and first and second obtuse marginal (OM) branches. Coronary angiography documented the patency of the vein graft and the occlusion of the mammary artery graft. The LAD appeared diffusely diseased (Figure 1A), and a percutaneous coronary intervention (PCI) was therefore performed, with two overlapping sirolimus-eluting stents (Cypher, Cordis, USA) successfully deployed at 1620 kPa (Figure 1B). Dual antiplatelet therapy with acetylsalicylic acid (160 mg/day) and clopidogrel (300 mg bolus, followed by 75 mg/day) was recommended and initiated. One week after the procedure, the patient experienced angina at rest, and a repeat angiography showed two nonocclusive thrombi inside the distal stent in the LAD (Figure 1C), with Thrombolysis In Myocardial

Une resténose précoce après l'implantation d'une endoprothèse à élution de médicament : Le rôle putatif de l'activation des plaquettes

Les endoprothèses à élution de médicament (EÉM) réduisent l'hyperplasie intinale et la resténose, mais elles inhibent également l'endothélisation de l'endoprothèse, rendant la surface vasculaire plus thrombogène. Le présent rapport décrit deux cas de resténose sur endoprothèse après l'installation d'une EÉM exactement au foyer où s'était produite la thrombose subaiguë sur endoprothèse coronaire. Un suivi très attentif s'impose lorsqu'on constate la possibilité d'une thrombose intraluminale causée par la resténose dans l'EÉM.

Infarction (TIMI) grade 3 flow. An infusion of abciximab (ReoPro, Centocor, USA) was initiated (0.25 mg/kg bolus over 3 min, followed by a 12 h infusion at 0.125 µg/kg/min); balloon PCI was then successfully performed. Three months later, the patient had a recurrence of symptoms, and a third angiography showed two focal in-stent restenoses located at exactly the same sites of the previous thrombi inside the LAD (Figure 1D). Intravascular ultrasound examination identified adequate stent expansion (Figure 1E-F). The patient underwent a repeat successful balloon PCI, and 12-month dual antiplatelet therapy was recommended. Nine months later, angiography showed full stent patency.

Case 2

A 72-year-old diabetic hypertensive woman with a previous lateral myocardial infarction underwent coronary angiography for effort angina. Diffuse, severe disease of the LAD was documented (Figure 2A), with a chronic occlusion of the distal left circumflex artery and an 80% ostial narrowing of the first OM branch. A staged PCI was planned, and acetylsalicylic acid (160 mg/day) and clopidogrel (75 mg/day) were started one week before the intervention. Abciximab was given in the catheterization laboratory as a bolus of 0.25 mg/kg over 3 min, followed by a 12 h infusion of 0.125 µg/kg/min. After a 2.0 mm balloon predilation, four overlapping paclitaxel-eluting stents (Taxus, Boston Scientific, USA) were deployed. However, after stent positioning, two small thrombi were detected in the mid-LAD (Figure 2B). Complete vessel patency was re-established with repeat 3.5 mm balloon dilations. A mild elevation of troponin I (peak 9 µg/L) and a normal creatine kinase (muscle-brain) level

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Figure 1 **A** Coronary angiography in the posteroanterior view showing a long lesion in the mid-distal left anterior descending coronary artery (LAD). **B** Two overlapping Cypher stents (Cordis, USA) (3.0/33 mm + 2.5/18 mm) were successfully deployed in the LAD. **C** An emergency coronary angiography performed one week later for unstable angina showed two small nonocclusive spheric thrombi (arrowheads) inside the distal stent of the LAD. Balloon angioplasty successfully restored vessel patency (not shown). **D** Three months later, repeat angiography performed for symptom recurrence documented two focal in-stent restenoses (arrows) located at the sites of both previous thrombi. In both cases, intravascular ultrasound documented complete stent expansion and severe neointimal hyperplasia (**E-F**)

were documented, and the patient was discharged after few days on dual antiplatelet therapy. Two months later, the patient was re-admitted for PCI of the OM branch; angiography at this time showed a focal restenosis, located exactly at the site where the proximal thrombus had been previously documented (Figure 2C). The OM branch was treated with a 12/3.0 mm Taxus stent, and the LAD lesion was redilated with a 3.5 mm balloon. Repeat angiography after 14 months showed persistent patency of the LAD, with no signs of restenosis (Figure 2D).

DISCUSSION

The findings described in the present report raise the possibility that the rare occurrence of early in-stent restenosis after DES deployment may be specifically linked to the occurrence of subacute stent thrombosis. Platelet activation has been frequently invoked as a possible mechanism of neointimal proliferation.

After the deployment of balloon-expandable stents, platelets cover the site of endothelial denudation, and platelet-rich mural thrombi form on the stent struts (5). Thrombin, produced on the surface of activated platelets within the platelet-rich thrombus, is a potent chemoattractant for circulating monocytes and may directly stimulate the proliferation of vascular smooth muscle cells (6). In addition,

Figure 2 **A** A very long lesion in the left anterior descending coronary artery was documented at angiography. **B** During the deployment of four overlapping Taxus stents (Boston Scientific, USA) (2.75/24 mm + 2.75/16 mm + 3.0/8 mm + 3.5/20 mm), two thrombi were detected inside the proximal stents (arrowheads). A good result was obtained with repeat 3.5 mm balloon dilations (not shown). Two months later, the patient was readmitted for the planned percutaneous coronary intervention of an obtuse marginal branch. **C** Angiography now showed a focal restenosis located at the site where the more proximal of the two thrombi was previously documented (arrow). The left anterior descending coronary artery was redilated with a 3.5 mm balloon. **D** Repeat angiography at 14 months documented the persistence of full vessel patency, with no signs of restenosis

the release of platelet-derived growth factors may contribute to smooth muscle cell chemoattraction (into the intima) and proliferation (7). The relevance of these mechanisms to the actual occurrence of stent restenosis has been strongly questioned because clinical trials have failed to document any efficacy of antiplatelets and anticoagulants in preventing restenosis (8,9).

DES reduce intimal hyperplasia and restenosis, but they also inhibit stent re-endothelialization, making the vessel surface more thrombogenic for longer time periods. Although infrequent (occurring as a subacute event in 0.7% of cases within 30 days after implantation and in 0.6% during the nine months following DES implantation [10]), stent thrombosis is a catastrophic event. The problem may be of a higher magnitude or an extended time course in the case of DES compared with bare metal stents (4). In addition, stent thrombosis with DES may be linked to a decreased efficacy of DES in preventing restenosis. In an animal model, Hwang et al (11) have shown that thrombus apposition within a DES creates large variations in drug elution, rendering drug delivery to the vessel wall unpredictable. The presence of a thrombus may therefore create a situation specific to DES, compared with bare metal stents, eventually being linked to the occurrence of neointimal hyperplasia and restenosis.

Extreme care to recognize thrombus formation is mandatory during DES implantation. When DES-PCI is planned, full antiplatelet therapy should be promptly initiated and subsequently continued for longer times than with bare metal stents; in our opinion, for at least nine months after the procedure (12). Careful patient follow-up is also necessary after the recognition of small intraluminal thrombi inside DES, even if the combined pharmacological and interventional treatment has been successful, because restenosis at the site of DES thrombosis may be more frequent than otherwise expected.

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