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CASE REPORTS

Multiple In-Stent Restenosis. A Rare Cause of Resistance to Antiproliferative Drugs?

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ABSTRACT

The introduction of novel stent designs and implantation techniques represents a significant milestone in percutanious coronary intervention. Despite continuous technological progress, the incidence of in-stent restenosis remains relatively high. An uncommon cause of in-stent restenosis is resistance/hypersensibility to antiproliferative drug, and although rare, it can lead to devastating short- and long-term results.

We present the case of a 50-year-old male, with multiple cardiovascular risk factors, who is admited to the Institute of Cardiovascular Diseases in Iași, Romania, for stable angina. Following coronarography, a percutaneous coronary angioplasty is performed with a Sirolimus stent for a 80% right coronary stenosis. Short-term evolution is marked by recurrent angina with an increase in severity of native atherosclerotic plaques from the left coronary and a complete occlusion of the right coronary stent. Multistenting (using Sirolimus stents) of LM, LAD and LCX was performed. After three months, all Sirolimus stents were restenosed or completely occluded. The patient was referred for surgical revascularization. A month later, he was admitted with anterior MI, and LIMA graft as occlusion at the anastomosis site with LAD was noted. LM-LAD angioplasty was performed (with Sirolimus stent). Short-term evolution was marked by a second anterolateral MI followed by LM-LCX angioplasty with Everolimus stent. After one year, the patient had mild angina, and coronarography revealed a permeable LM-LCX Everolimus. Malignant in-stent restenosis following implantation of multiple stents with the same antiproliferative drug can be a significant indicator for a genetic resistance/hypersensibility. Although there are no markers to predict this entity, its incidence is very low, but it is associated with poor long-term outcomes.

Keywords: multistenting, resistance, hypersensibility, in-stent restenosis..

INTRODUCTION

Drug eluting stents were conceived as the next step after balloon angioplasty and bare metal stents for tackling the entity of neointimal hyperplasia. Although there are numerous well-known factors linked to in-stent restenosis, a rare cause is the resistance to antiproliferative drugs (1). The underlying mechanism of action and causes to resistance to paclitaxel and sirolimus are well documented in cancer literature and can be either present genetically (mutation to mTor gene) or be acquired with cytotoxic exposure to antiproliferative agents (2).

CASE REPORT

We present the case of a 50 year old male known with stable coronary artery disease for three years, who is admitted to "George I. M. Georgescu" Institute of Cardiovascular Diseases, Iasi, for angina with mild exertion for two weeks, with a duration of 10-15 minutes, and with total relief with two sprays of nitroglycerin.

From the medical history we retain a stable angina with mild exertion (CCS II) with multiple negative non-invasive stress-tests, a long-standing well controlled grade 3 hypertension, mild hypercholesterolemia, and a high tobacco exposure (40 pack years). The patient has the following

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chronic medical treatment: Olmesartan 40 mg/day and Amlodipine 10 mg/day (Sevikar), Bisoprolol 5 mg/day, Atorvastatine 10 mg/day and Aspirin 75 mg/day. The physical examination reveals grade I abdominal obesity and normal blood pressure (BP), without any significant difference between upper extremities.

The laboratory tests show a mild mixed dyslipidemia (LDL-cholesterol 150 mg/dL, total cholesterol 219 mg/dL, triglycerides 149 mg/dL) and impaired fasting glucose (glycemia 115 mg/dL). EKG reveals sinus rhythm with a heart rate of 65 bpm and normal QRS morphology. Echocardiographic parameters are within normal range, without contraction abnormalities and a normal global systolic function, ejection fraction (EF) of 60%.

The patient performs a cyclo ergometer test, which is positive for angina (Kattus 3) and ischemia with a high Duke risk score. Coronarography reveals 80% ostial stenosis of right coronary artery (RCA) with presional damping at intubation, and atherosclerotic plaques in LAD II and LM without hemodinamic significance. Direct angioplasty with a 4.5/19 mm drug eluting stent (Biomime) is performed for the RCA lesion with excellent result (Fig. 1). The short-term evolution is favorable with complete remission of anginal pain and the patient is discharged after two days.

After four months, the patient presents to the emergency department for angina at rest and mild exertion. The EKG and echocardiographic parameters are within normal range and myocadial enzymes are normal. Coronarography reveals 50% LM stenosis and long 75% LAD I-II lesion and a permeable RCA stent with no in stent restenosis. Predilatation with a 3.0/20 mm baloon is performed in the middle-proximal part of LAD and a drug elluting stent 3.5/48 mm (Biomime) is implanted in LAD II. A second 4.0/23 mm drug elluting stent (Biomime) is implanted in LM-LAD I, with excellent result (Fig. 2). The patient is discharged with complete remission of angina.

After one month, the patient is admitted in the emergency department with acute NSTEMI (Tn I 1 ng/mL, CK-MB 80U/L) with ST depression in V4-V6. Echocardiography reveals severe hypokinesia of 2/3 apical anterior wall, 1/3 apical lateral wall and 1/3 apical septum with a moderate depressed global systolic function (EF 35%). Coronarography shows: 90% in-stent ulcerated stenosis at distal LM with extension to ostial LAD, a 99% ulcerated in stent stenosis in LAD II (Fig. 3), with chronic total occlusion of the ostial RCA stent. Ballon angioplasty with a 3.0/15 mm ballon is performed for the lesion in LAD II and the patient is admitted to cardiovascular surgery department with the indication of coronary artery by-pass. The next day, triple aorto-coronary bypass is performed with: Y anastomosis of left internal mamary artery (LIMA) and right internal mamary artery (RIMA) at LAD and obtuse marginal I (OM), and left internal saphenous vein (SVG) anastomosis to RCA, with excellent result. The patient is discharged with complete remission of anginal pain.

After one month, the patient is admitted to the emergency department for anterolateral STEMI (Tn I 1,3 ng/mL, CK MB 98 U/L and EKG type A wellen pattern in V2-V4). Echocardiographic fin-

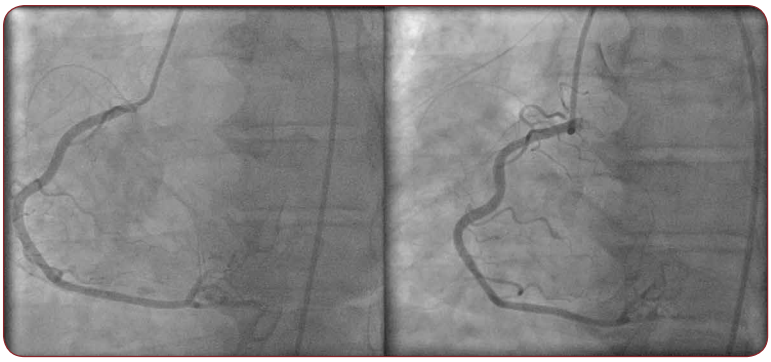

FIGURE 1. 80% ostial RCA stenosis. PCI with 4.5/19 mm Biomime stent

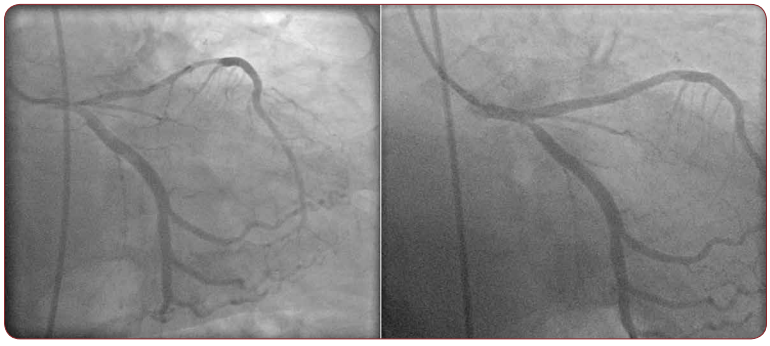

FIGURE 2. 40% stenosis of LM and 75% long LAD I-II stenosis. Angioplasty with 4.0/23 mm Biomime LM-LAD I and 3.5/48 mm Biomime LAD II

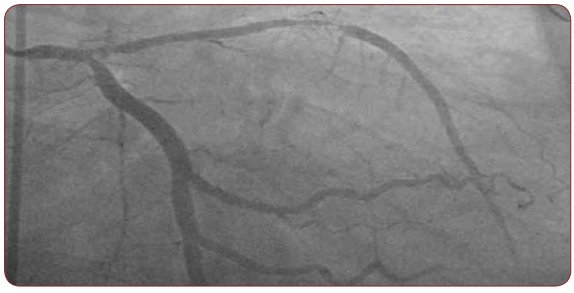

FIGURE 3. In-stent restenosis 90% distal LM and 99% LAD II

dings show akinesia of the 2/3 apical anterior wall, 2/3 apical septum and 1/3 lateral wall with a severe depressed global systolic function (EF 25%) and moderate secondary mitral regurgitation. Urgent coronarography reveals: 80% stenosis of distal LM, complete ostial occlusion of LAD, 95% ostial stenosis of left circumflex (LCX). The SVG is permeable without restenosis. LIMA angiography objectify a 99% stenosis at the Y anastomosis and 99% stenosis at the anasomosis of LIMA to LAD. Percutaneous revascularisation of LIMA lesions is attempted but the patient develops acute pulmonary edema and cardiogenic shock (oxygen saturation of 70%, 70/50 mm Hg BP and 110 HR) and is transferred to the intesive care unit. Oro-tracheal intubation and mechanical ventillation with intravenous inotrope support (Dobutamine and Noradrenaline) is performed. A raise in myocardial enzymes is notted (CK MB from 98 to 153 U/L) and the patient is redirected to cathlab. Coronarography reveals complete LIMA closure at the Y anastomosis. Angioplasty of the native left coroanary lesions is performed: dilatation with 3.0/25 mm ballon of LAD II, implantation of 4.5/16 mm drug elluting (Biomime) stent is implanted from LM to LCX, and a Kissing postdillatation with a 4.0/20 mm ballon from LM to LCX and 3.5/15 mm ballon from LM to LCX and complete repermeabilisation of LAD and LCX with TIMI 3, MBG 3 distal flow was obtained (Fig. 4). After three days, the patient is detubated with gradually reduction of intravenous inotropic support, with a good short-term evolution. Echocardiography reveals the same kinetic disturbances with a EF of 30%. Considering the malignant evolution of the in stent restenosis and progression of the atherosclerotic lesions trombophillic tests, ANA antibodies and antiphospholipidic antibodies are evaluated with negative results. The patient is discharged after two weeks with moderate exertion dyspnea.

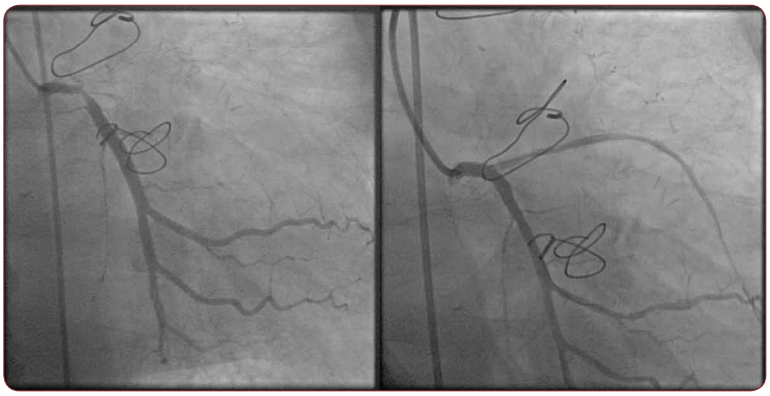

FIGURE 4. Repermeabilisation of LAD

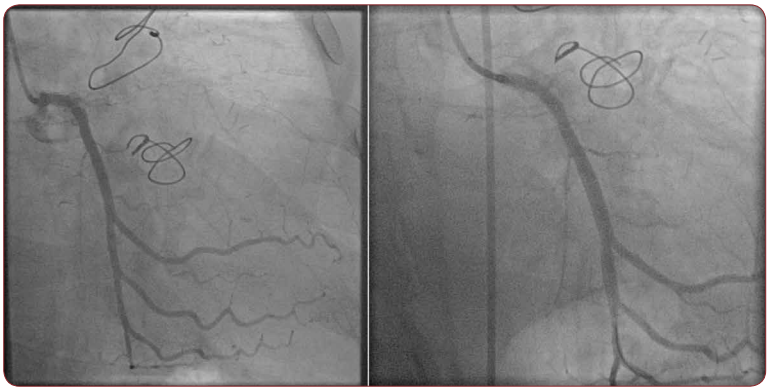

FIGURE 5. LCX restenosis 99%. Balloon angioplasty ostial LCX

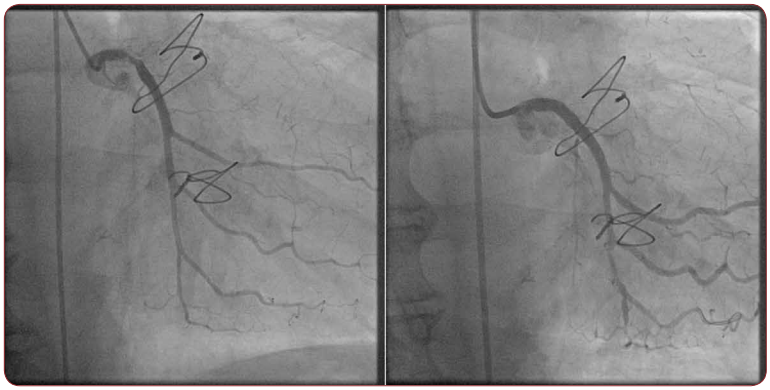

FIGURE 6. 99% ostial restenosis LCX. PCI with 4.5/15 mm Promus stent LM-LCX

After three months, the patient is readmitted to emergency department for unstable angina. EKG reveals ST depression in lateral leads with ST elevation in aVR. Myocardial enzymes were within normal range. Coronoragraphy objectify complete ostial occlusion of LAD and 95% in stent restenosis of LCX. Ballon angioplasty with 3.5/15 mm ballon at the ostium of the LCX is performed with excellent result (Fig. 5.). The SVG is permeable without restenosis. The patient is discharged with moderate exertion dyspnea and without angina.

After one month, the patient is admitted to emergency department for unstable angina. EKG reveal ST depression in lateral leads, and myocardial enzymes are within normal range. Coronarography reveals ostial suboclusion of LCX. Direct angioplasty with 4.5/15 mm drug elluting stent (Promus) is performed from LM to LCX with excellent result (Fig. 6). The patient is discharged with moderate exertion dyspnea without angina.

RESULTS

The long-term evolution favourable, with no angina at 6 and 12 months after the last angio-

plasty, with moderate exertion dyspnea. Echocardiography revealed moderate systolic disfunction (EF of 35%) with akinesia of apical 2/3 anterior wall, apical 2/3 lateral wall, and apical 2/3 septum.

DISCUSSION

In-stent restenosis represents the lumen diameter decrease following percutaneous coronary intervention with stent implantation. This phenomenon occurs due to neointimal proliferation or neoatherosclerosis (1). The clinical presentation following in-stent restenosis is recurrence of angina symptoms or an acute coronary syndrome, and may drive to reintervention either with stent or balloon angioplasty or coronary artery by-pass (3). The exact incidence of in stent restenosis is not well known due to the multiple types of stents available and multiple risk factors associated with this phenomenon.

Restenosis is a progressive event that begins in the early hours after the barotrauma determined by the percutaneous coronary intervention and is classified in early (within days), late (weeks to months) and very late (after one year) (4).

A rare cause of in-stent restenosis is resistance to antiproliferative drugs. Resistance to paclitaxel and sirolimus are well-described in the cancer literature. The underlying mechanism is represented by polymorphisms in the genes that encode mTOR or proteins involved in paclitaxel or sirolimus metabolism leading to decreased binding of sirolimus to mTOR or FK-B12 (2, 5). This resistance may be genetically predetermined or aquired following the cytotoxic insult after the exposure to the drug (6). A secondary cause that may increase the rate of restenosis in a drug-resistant patient is the persistence of the inflammatory response beyond 90 days after arterial inury. The pattern of restenosis seen in this situations is usually focal, and occurs usually between one day and 90 days (6).

In our case, the patient experienced multiple in-stent restenosis requiring repeat target vessel revascularisation following the implantation of multiple sirolimus stents, but not after the implantation of a everolimus stent (the last stent implanted was permeable, without in-stent restenosis at six months. Currently, there are no laboratory tests for the detection of resistance to sirolimus, and the diagnosis is usually made from the clinical presentation and evolution after angioplasty.

Although our patient presents numerous other risk factors associated with restenosis: stent lenght of 125 mm, overlap of two stents in LCX and LM, LIMA restenosis; the pattern of the restenosis was focal, and became clinical significant at one to four months (1-2 months following LAD PCI, 1-3 months LCX PCI and four months after RCA PCI), the temporal pattern of restenosis following sirolimus stents implantation, persistence of raised C reactive protein over 90 days and absence of restenosis following the implantation of everolimus stent at 12 months all favour the possibility of a genetic resistance to sirolimus.

CONCLUSION

In-stent restenosis of drug elluted stents, or "DES failure", represents a major cause of repeat target vessel revascularisation and is associated with increased mortality and morbidity. A rare cause of in-stent restenosis is represented by resistance to antiproliferative (sirolimus and paclitaxel) agents and is caused by genetically predetermined or acquired mutations in the mTOR and FK-B12 genes. ❑

Conflicts of interest: none declared.
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