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Two Times In-stent Restenosis in a Diabetic Female Patient Treated using a Paclitaxel Eluting Balloon

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Abstract: ***In- stent restenosis (ISR) remains a significant clinical problem especially in patients with multiple risk factors .With the introduction of drug-eluting stents (DESs), there has been a considerable reduction in the in-stent restenosis rates and target lesion revascularization. Nevertheless patients with multiple risk factors continue to show increased rates of restenosis and late lumen loss. We report a case of a 58 year-old woman who presented with an in-stent restenosis and benefited from a successful PCI using a Drug coated balloon.***

Keyword: in-stent restenosis, Drug coated ballon, Drug-eluting stents

1. Introduction

In- stent restenosis (ISR) remains a significant clinical problem especially in patients with multiple risk factors [1,2] .With the introduction of drug-eluting stents (DESs), there has been a considerable reduction in the in-stent restenosis rates and target lesion revascularization. Nevertheless patients with multiple risk factors continue to show increased rates of restenosis and late lumen loss [3]. Systemic treatments with antiplatelet drugs, statins, angiotensin-converting enzyme inhibitors ,or calcium-channel blockers have not shown to be effective in reducing neointimal proliferation [4,5,6].

We report a case of a 58 year-old woman who presented with an in-stent restenosis and benefited from a successful PCI using a Drug coated balloon.

2. Case Report

A 58 year-old female patient, diabetic on insulin therapy. The patient presented with a stage II of effort inducing angina in October 2013, coronary angiography objectified tight stenosis of Left descending artery's the middle segment and a percutaneous coronary intervention was performed , in another center, using a first generation drug eluting stent (DES) .

One year later, she began to have a stage IV effort inducing angina. She was refered to our center where a second coronary angiography was performed, showing a mild in-stent restenosis. The decision was to optimize anti-ischemic treatment associating DAPT (dual antiplatelet therapy), statins, betablocker, angiotensin-converting inhibitor enzyme, molsidomine and Trimetazidine. Due to angina persistence, we performed a PCI using a second generation DES that was successfully placed.

However, even with optimal anti-ischemic medical treatment, the effort inducing angina reappeared in 2016 and went from stage II to stage IV. Physical examination was normal, electrocardiogram showed no modifications and biology tests revealed LDL-cholesterol level at 0,99 g/l, HDL-cholesterol at 0,54 g/l HbA1c at 12,4% with a good renal function.

A stress test was indicated and performed but the results were not concluding, we decided then to explore by coronary angiography that revealed in-stent restenosis (Figure 1). Percutaneous coronary intervention was done using a paclitaxel coated balloon, the procedure was very smooth and immediate results were satisfying (Figure 2).

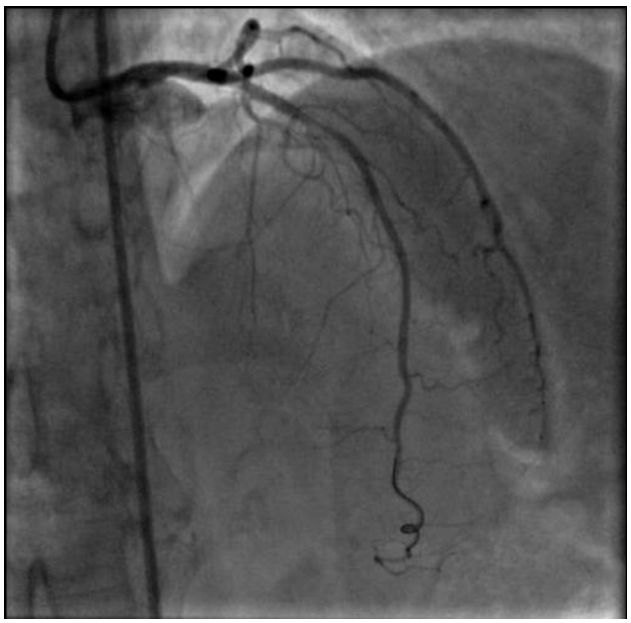

Figure 1: Coronary angiography image showing in-stent restenosis in the middle segment of left descending artery

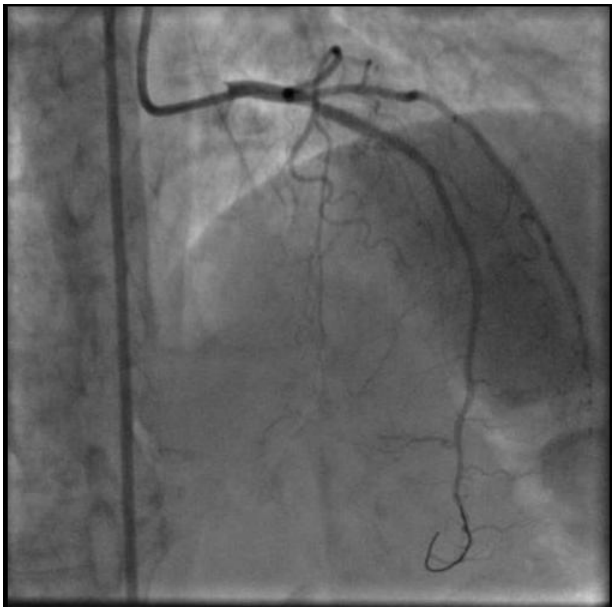

Figure 2: Coronary angiography image immediately after angioplasty of in-stent restenosis using a drug eluting balloon

The patient was discharged with medical treatment associating clopidogrel, aspirin, atorvastatin and bisoprolol, Ramipril was stopped due to a low blood pressure. In a follow-up of 24 months, our patient is stable and asymptomatic.

3. Discussion

In-stent restenosis (ISR) has always been considered the "enemy" for the interventional cardiologists, motivating different technical improvements in order to reduce its occurrence: firstly, newer generation bare metal stents (BMS), then drug-eluting stents (DES) [8] and finally drug-coated balloons (DCB) [9, 10].

Restenosis is defined as a reduction in lumen diameter after percutaneous coronary intervention (PCI), either with or without stent implantation. In case of no-stent strategy, it usually consists in vessel remodeling and elastic recoil (ER); otherwise it is determined by an excessive tissue proliferation in the luminal vessel of the stent called "neointimal proliferation", or by a new-occurring atherosclerotic process called "neoatherosclerosis" [11, 12].

Among the clinical factors for ISR, diabetes emerges as the most important risk factor for aggressive neointimal proliferation [13]. The typical prothrombotic environment of diabetic coronary vessels, including increased blood viscosity, decrease in biological activity of antithrombin II, fibrinogen and factor VIII and enhanced platelet aggregation, could play a role in this phenomenon [14,15]. Furthermore, the effect of stimulatory growth factors like insulin-like growth factor-1 on VSMCs may cause a greater degree of neointimal hyperplasia [16]. Atherectomy specimens from restenotic lesions in diabetic patients showed no increased proliferation of the smooth muscle, but rather a greater fibrotic response which may lead to vessel constriction. In a study leaded by Kitoga et al, in-stent restenosis remained a potential risk for coronary diabetic patients treated with drug-eluting devices; they also concluded that male gender, oral therapy for diabetes and stent diameter were found to be predictors for in-stent restenosis [17].

Several factors determine an inhomogeneous drug distribution promoting the ISR process: vessel and lesion characteristics (a tortuous segment, a calcified vessel, a different caliber of the vessel segment or bifurcation lesions), possible stent struts fractures and finally stent underexpansion [18]. Also, an adventitial contraction known as *Remodeling* along with persistent inflammation, intimal and medial dissections post-PCI, and elastic recoil upon balloon dilatation all contribute to restenosis [19].

Stent length is an important determinant for ISR as well; in fact longer stents are an important risk factor for restenosis and ST. Choi in a study with median follow-up of 36.9 months observed how patients treated with stent length ≥32 mm had a greater risk of ISR than those treated with a stent <32 mm [20]. Finally, also vessel diameter plays an important role: as reported by the HORIZONS-AMI study, ISR rate increases significantly when the vascular caliber is ≤3 mm [21].

The introduction of DES has drastically reduced the occurrence of severe neointimal proliferation, the dominant cause of ISR. This decrease translated into important reductions in TLR [22]. Newer DES are considered safer than the first generation DES [23].

Our patient benefited from a PCI using a first generation of DES back in 2013, the first in-stent stenosis was treated by a second generation DES in 2015, and the second in-stent stenosis was treated by a Paclitaxel eluting balloon.

To this day, the real innovation for the treatment of ISR, as also underlined by current guidelines, is represented by the use of DCB, both for the treatment of DES and BMS ISR: here this technology gained a role similar to DES (class I, level of evidence A) [24].

Historically, ISR represented the first clinical application for DCB. From the pathophysiological point of view, currently available DCB elute paclitaxel, a drug that effectively inhibit smooth muscle cells proliferation and migration by irreversibly stabilizing intracellular microtubules, thus blocking cell replication during the metaphase and anaphase stages of mitosis. The advantages of this drug include a high lipophilia, a relative selectivity for smooth muscle cells and cytotoxic action limited for a few days only [25].

DCB resulted the second most effective treatment,Siontis et al published a meta-analysis, concluding that "two strategies should be considered for treatment of any type of coronary ISR: PCI with everolimus-eluting stents because of the best angiographic and clinical outcomes, and DCB because of its ability to provide favourable results without adding a new stent layer" [26].

4. Conclusion

In-stent restenosis is the most common complication of PCI and presents a real challenge to interventional cardiologists. It is a multifactorial pathology that implicates both the patient's genetics and the stent characteristics. DCB seemed to be the convenient choice of revascularization in the case of our patient and the results seem to be satisfying.

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