REPETITIVE STENT FRACTURES WITH DIFFUSE CORONARY ARTERY MICROANEURYSM FORMATION – SIROLIMUS ELUTING STENT HYPERSENSITIVITY?

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SUMMARY – While drug eluting stents (DES) are being more widely used in ever more patients receiving DES each day, some new complications may be emerging. Stent fractures and hypersensitivity reactions to stents are among recognized complications that can lead to therapeutic dead end from the interventional cardiologist's point of view. We present a case in which we reached therapeutic dead end with a sirolimus eluting stent, i.e. repetitive stent fractures with diffuse microaneurysms along the implanted DES, possibly due to hypersensitivity reaction to parts of the stent.

Key words: *Coronary stent restenosis; Prosthesis failure; Drug eluting stents; Hypersensitivity, polymer; Coronary aneurysm*

Introduction

Drug eluting stents (DES) have been ever more widely used since their first introduction in 2000[1,2]. After first studies, a sirolimus eluting stent (SES; Cypher) was approved in Europe in 2002 and by the Food and Drug Administration (FDA) in the USA in 2003. Until today, over 3 000 000 sirolimus eluting stents have been implanted in the world[3].

Since then, some negative features regarding safety of the first generation DESs have been reported, with late and very late stent thrombosis certainly as most extensively explored, and on the other hand, the possible hypersensitivity to SES as underestimated one. Although there are case reports in the literature as well as reports from the FDA and the Research on Adverse Drug events and Reports (RADAR), the real incidence, prevalence and consequences of hypersensitivity to DES are not known, as well as the possible role in some cases of stent thrombosis[4,5]. We describe a patient who developed repetitive stent fractures, in-stent restenosis and diffuse coronary artery wall dilatation with the risk of stent thrombosis, all possibly caused by DES hypersensitivity.

Case Report

We present a 62-year-old female patient with a history of hyperlipidemia and coronary artery disease, who underwent several coronary angiographies with interventions on RCA and LAD. The patient was first treated with 2 SESs in LAD, and then 6 months later with 2 bare metal stents in RCA. One year after the first procedure, coronary angiography performed due to positive ECG stress test showed focal fracture of distal sirolimus stent in the LAD with aneurysm formation, which was successfully treated with graft stent implantation[6].

During routine follow-up at 3 and 6 months after graft stent implantation, the patient was symptom free and had negative ECG stress. One year after the implantation, the patient was admitted because of a positive ECG stress test, although she still remained symptom free.

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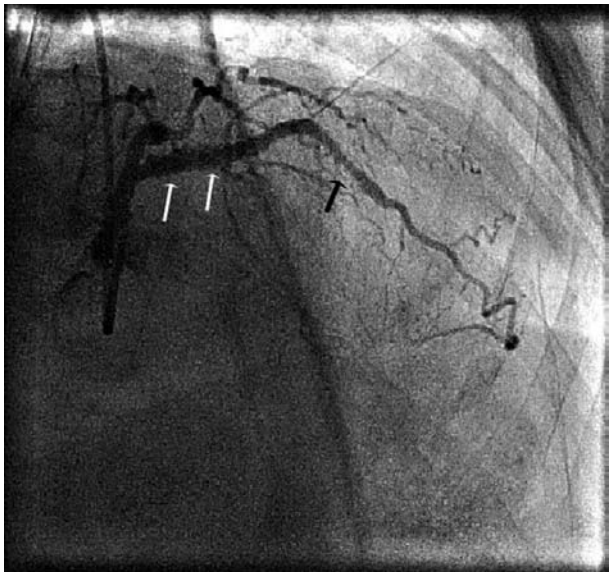

Fig. 1. RAO cranial view showing 50% in-stent restenosis in graft stent implanted in LAD and arterial dilatation with microaneurysms along the previously implanted sirolimus eluting stent.

Upon admission and routine preparation, the patient underwent coronary angiography, which showed RCA with no in-stent restenosis, while LAD showed 50% in-stent restenosis in the graft stent implanted one year earlier, new stent fracture proximally (SES implanted two years before), and diffuse microaneurysmatic changes with delayed contrast filling along previously implanted proximal SES. Angiography also revealed slow flow (TIMI II-III) in LAD distally to implanted stents (Figs. 1-4).

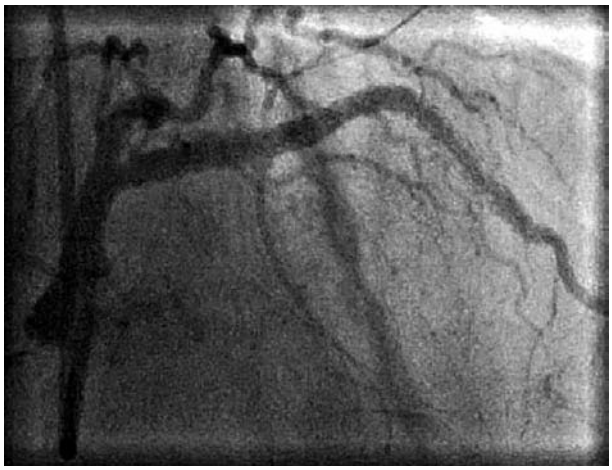

Fig. 2. RAO cranial view enlarged.

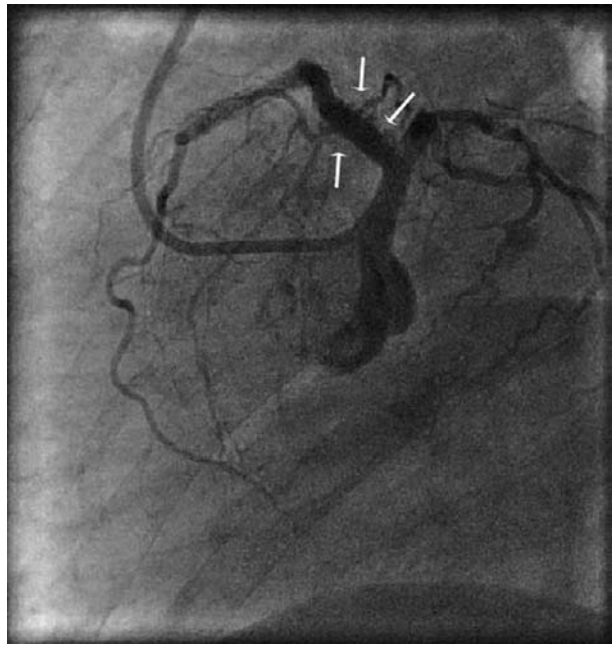

Fig. 3. LAO caudal view showing arterial dilatation with microaneurysms of the proximal LAD.

Because the patient underwent two interventions on the LAD with two SES implantation and graft stent implantation in previous fracture, further percutaneous intervention on the LAD was not reasonable. The only remaining therapeutic option was coronary artery bypass surgery. Although coronary bypass would have solved ischemia in the LAD per-

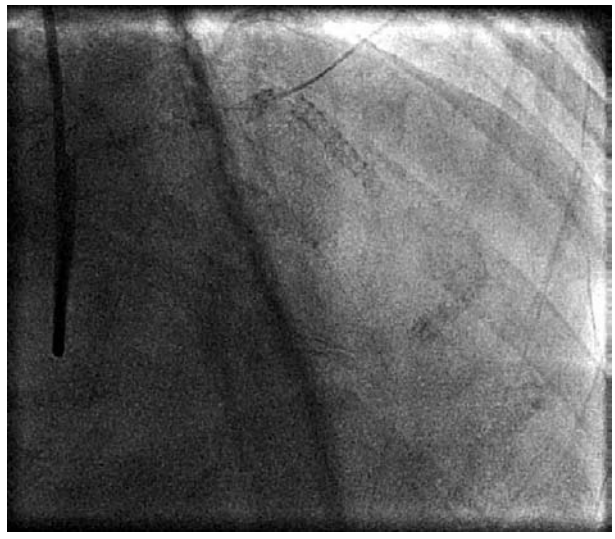

Fig. 4. RAO cranial view of the fractured stent.

fusion area, there would still remain the risk of in-stent thrombosis with the loss of a substantial area of viable myocardium. We had reached a therapeutic dead end.

The patient was informed of the finding and on the possible need of cardiac bypass surgery and all peri- and postoperative risks. Since the patient was asymptomatic, she decided to postpone the surgery for some time.

She was discharged from the hospital several days later with dual anti-aggregation therapy (DAT) with aspirin and double dose clopidogrel, high dose statin, beta blocker, long acting nitrate and trimetazidine, with a recommendation for regular, frequent follow-ups.

Discussion

The key message of this report is to point out that with implantation of DES, a therapeutic cul-de-sac could be reached and could potentially lead to the worst possible outcome. In a previous report, we presented a patient with stent fracture and coronary artery aneurysm and described the incidence according to the literature, the possible mechanisms and therapeutic options for stent fractures[6]. We have now found that the same patient has a new stent fracture in previously implanted SES with arterial dilatation and multiple aneurysmatic changes of the LAD along the whole length of previously implanted SES. The first stent fracture occurred in distal SES, whereas the new fracture is in the proximal one. Of importance is that proximal stent was not overinflated with non-compliant balloon, nor was it implanted in the area of LAD "bridging", both of these regarded as risk factors for first stent fracture.

While stent fracture could be explained by mechanical factors (longer and overlapping stents, Cypher stent implantation, excessive high pressure postdilatation, right coronary artery intervention, myocardial bridging and procedure in tortuous lesions)[7-10], the etiology of repetitive stent fractures in the same patient with diffuse arterial dilatation and microaneurysmatic changes is more complex.

Because changes seen on the last angiogram are diffuse along the whole length of proximal SES and could not be found along other parts of LAD or along bare metal stents in the RCA, one possible explanation is reaction to components of SES (Cypher, Cordis Johnson & Johnson).

Since our patient has normal leukocyte count with normal eosinophils, we can only assume a hypersensitivity reaction to her DES based on clinical and angiographic findings, bearing in mind previous reports and findings[10].

In this particular case, there is evidence for three stent-driven complications: a stent fracture that is a mechanical event, aneurysmal arterial dilatation that is probably caused by inflammatory response and consequential arterial wall weakening, and in-stent restenosis, which is not frequent event with DES. After detailed case analysis and literature review, several issues remain unsolved: first, which component of the stent is the causative trigger; second, which event was initial; and third and most important, what is the optimal treatment approach for our patient.

The suspected hypersensitivity reaction could be to the metallic stent, polymer or sirolimus. Cypher stents have 0.0055" thick 316L stainless steel struts and are coated with a layer of a poly-n-butyl methacrylate and polyethylene-vinyl acetate copolymer containing 140 μg sirolimus (Wyeth-Ayers)[11].

The first possibility is a hypersensitivity reaction to nickel or molybdenum from the stainless steel of the metal struts, but previous studies have not shown hypereosinophilic reactions in human autopsies over 400 BMS[10] . Also, the patient has no changes along BMS implanted in RCA.

Sirolimus is the other possible cause of hypersensitivity reaction, although it usually reduces eosinophilic infiltration and is associated with low levels of hypersensitivity[4]. Also, since 80% of sirolimus is released in the first 30 days and the drug is undetectable in arterial wall after 60-90 days according to animal studies[11], a reaction to sirolimus in our patient is highly unlikely (the patient underwent coronary angiography 6 and 12 months after the first procedure, and diffuse arterial changes were not detected).

On the other hand, late hypersensitivity to DES with possible reaction to polymer has been described[10], with arterial wall dilatation as a positive arterial remodeling provoked by inflammatory reaction. Also, a review of cases by the RADAR from 2006 has identified 262 cases with hypersensitivity symptoms in patients with DES[4]. Among these cases, 17 were identi-

fied as certainly or probably caused by DES, and 14 of these by Cypher. Four patients had in-stent thrombosis and died, and pathology reports are the strongest evidence of DES causing hypersensitivity reactions. Pathology report from the case reported by Virmani *et al*. showed aneurysmally dilated artery with extensive inflammatory infiltrate of the intima, media and adventitia with medial destruction. Infiltrates consisted of lymphocytes, plasma cells, macrophages and eosinophils[10].

Regarding therapeutic options, as we said before, we decided to discharge the patient with DAT, postponing the decision on revascularization. Although the patient is asymptomatic, we have strong evidence of LAD territory ischemia and indication for ischemia-driven target vessel revascularization. Additional percutaneous revascularization is not an option because we do not have evidence for the safety of additional DES with a different drug and polymer, and we assumed that it could be deleterious for the patient. There is an option for treatment of in-stent graft restenosis with drug eluting balloon, but this is probably not culprit lesion for ischemia. On the other hand, coronary artery bypass graft with a mammary artery offers the optimal solution for ischemia, but we cannot predict the development of further aneurysmal dilatation with the possibility of in-stent thrombosis and/or aneurysm rupture.

Although some reports describe regression or attenuation of hypersensitivity symptoms after therapy with corticosteroids, none of them included patients with focal reaction and arterial wall dilatation[4]. So, the option of corticosteroid administration remains open because it could be life-saving, but with several reasons for caution; we could not prove an inflammatory or hypersensitivity reaction by any laboratory test or imaging technique and corticosteroids could accelerate pre-existing atherosclerotic disease. This is why, at this moment, we have decided not to start the patient on steroids, but the wisest solution could be to schedule the patient for bypass surgery, with intraoperative biopsy, and in case of positive hypersensitivity to start corticosteroid administration with the intention to stop dilatation progression.

This case shows the need of close and careful follow-up of patients treated with DES, thinking of possible complications and diagnosing them on time.

References

1. SOUSA JE, COSTA MA, ABIZAID AC, RENSING BJ, ABIZAID AS, TANAJURA LF. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. Circulation 2001;104:2007-11.
2. MORICE MC, SERRUYS PW, SOUSA JE, FAJADET J, BAN HAYASHI E, PERIN M, *et al*. RAVEL study group, Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. Cordis. "www. cordis.com/products/cypher-sirolimus-eluting-coronary-stent". Cordis Corporation 2002-2010. 155-7118-16. December 10, 2010.
3. NEBEKER JR, VIRMANI R, BENNETT CL, HOFFMANN JM, SAMORE MH, ALVAREZ J, *et al*. Hypersensitivity cases associated with drug eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. J Am Coll Cardiol 2006;47:175-81. Epub 2005 Dec 1.
4. FDA advises physicians of adverse events associated with Cordis Cypher coronary stents. US Food and Drug Administration Public Health Web Notification. October 29 2003;T03-T71.
5. ŠTAMBUK K, PAVLOVIĆ N, GABRIĆ ID, KRČMAR T, TRBUŠIĆ M, MANOLA S. Coronary artery stent fracture with in-stent restenosis and aneurysm formation: diagnosis and successful treatment with graft stent implantation. Int J Cardiol 2010 May 26. [Epub ahead of print].
6. NAKAZAWA G, FINN AV, VORPAHL M, LADICH E, KUTYS R, BALAZS I, *et al*. Incidence and predictors of drug-eluting stent fracture in human coronary artery: a pathologic analysis. J Am Coll Cardiol 2009;54:1924-31.
7. UMEDA H, GOCHI T, IWASE M, IZAWA H, SHIMIZU T, ISHIKI R. Frequency, predictors and outcome of stent fracture after sirolimus-eluting stent implantation. Int J Cardiol 2009;133:321-6. Epub 2008 Mar 14.
8. MANOLA Š, PINTARIĆ H, PAVLOVIĆ N, ŠTAMBUK K. Coronary artery stent fracture with aneurysm formation and in-stent restenosis. Int J Cardiol 2010;140:e36-9. Epub 2008 Dec 23.
9. VIRMANI R, GUAGLIUMI G, FARB A, MUSUMECI G, GRIECO N, MOTTA T, *et al*. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation 2004;109:701-5. Epub 2004 Jan 26.
10. SUZUKI T, KOPIA G, HAYASHI S, *et al*. Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. Circulation 2001;104:1188-93.
11. KLUGHERZ BD, LLANOS G, LIEUALLEN W, KOPIA GA, PAPANDREOU G, NARAYAN P, *et al*. Twenty-eight-day efficacy and pharmacokinetics of the sirolimus-eluting stent. Coron Artery Dis 2002;13:183-8.

Sažetak

OPETOVANE FRAKTURE STENTA UZ NASTANAK DIFUZNIH MIKROANEURIZAMA KORONARNE ARTERIJE – PREOSJETLJIVOST NA STENT KOJI IZLUČUJE SIROLIMUS?

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Dok se stentovi koji ispuštaju lijekove sve više primjenjuju kod bolesnika svakodnevno, moguća je pojava novih komplikacija. Prijelomi stenta i reakcije preosjetljivosti na stentove neke su od poznatih komplikacija koje mogu dovesti do terapijski bezizlazne situacije sa stajališta intervencijskog kardiologa. Prikazuje se upravo takav slučaj sa stentom koji izlučuje sirolimus, gdje su nastupili opetovani prijelomi stenta uz difuzne mikroaneurizme duž ugrađenog stenta, moguće zbog reakcije preosjetljivosti na dijelove stenta.

Ključne riječi: *Koronarni stent, restenoza; Proteza, otkazivanje; Stentovi koji izlučuju lijek; Koronarna aneurizma*