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Case report

In-stent restenosis: neointimal priliferation or neoatherosclerosis

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Abstract In-stent restenosis, according to the time of occurrence presents itself as: earlywithin 24 hours; subacutewithin the first month; latewithin the first year; and very lateafter the first year.
A 72yearold female patient, D.Đ., was referred for rescue PCI (Percutaneous Coronary Intervention) after fibrinolysis for anteriorwall STEMI. Coronary angiography showed subocclusive lesions in the Cx (Circumflex artery) and LAD (Left Anterior Descendent), as well as a significant lesion in the RCA (Right Coronary Artery). A Synergy 3×16 stent at 12 atm was placed in the Cx, and a Synergy 3.5×16 stent at 10 atm in the LAD.
After six months, she was re-hospitalized for anterior-wall NSTEMI (Non-ST Elevation Myocardial Infarction). Coronary angiography revealed in-stent restenosis in the Cx and LAD, which were treated with post-dilatation using an NC Mozec 3.5×18 balloon.
Four months later, recurrent chest pain occurred. Coronary angiography showed subocclusive restenosis in the Cx. IVUS (Intravascular Ultrasound) demonstrated the presence of calcium behind the stent and neointimal proliferation within the stent. IVL (Intravascular Lithotripsy) was performed with a 3.5×15 balloon for 4 cycles. A DEB (Drug-Eluting Balloon) Elutax 3.5×20 was applied to the stent and proximal Cx for 55 seconds.
After eight months, another coronary angiography was performed due to reoccurring chest pain and a subsequent positive exercise stress test. Coronary angiography again showed a subocclusive lesion in the Cx stent, managed with a 3.5×16 NC balloon. Due to recurrent in-stent restenosis despite successful calcium removal with IVL and the presence of neointimal proliferation seen on IVUS, colchicine 0.5 mg daily was added for one year.
After one year, control coronary angiography again revealed in-stent restenosis in the Cx. Repeat IVUS this time demonstrated a small thrombus and areas of neoatherosclerosis as the mechanism of restenosis. Due to the neoatherosclerotic changes, the in-stent stenosis was treated with repeated IVL using a 3.5×15 balloon for all 12 cycles, and implantation of a new Synsiro 3.5×15 stent.
In-stent restenosis, based on the timing of presentation, may be acute, subacute, late, or very late. Mechanisms of in-stent restenosis, according to the time of onset, may include thrombosis, neointimal proliferation, and neoatherosclerosis. Regardless of timing, therapeutic approaches include balloon dilatation, application of a DEB, or implantation of a DES. Only in cases of proven neointimal proliferation additional oral therapy with colhicine, methotrexate or sirolimus should be considered, or parenteral administration of paclitaxel.

Key-words In-stent restenosis, thrombosis, neointimal proliferation, neoatherosclerosis

Introduction

In-stent restenosis has been a persistent issue since the introduction and use of stents. With the advent of new-generation stents made from improved alloys, with thinner struts and higher-quality polymers carrying antiproliferative drugs, this problem has become significantly less commonnow occurring in about 2% of implanted stents in the left main coronary artery after 2 years of follow-up[1], or 0.8% in patients with DES and 1.2% (P = 0.0498) in patients with BMS after 6 years of follow-up[2].

In-stent restenosis, based on the time of onset, can be classified as: **Early-**within 24 hours; **Subacute-**within the first month; **Late-**within the first year; and **Very late-**after the first year.The development of in-stent restenosis is influenced by patientrelated factors such as stent implantation during ACS (Acute Coronary Syndrome) or premature discontinuation of DAPT (Dual Antiplatelet Therapy). Other patient related factors, like diabetes mellitus, age, smoking, malignancy, heart failure, and renal failure directly or indirectly contribute to accelerated atherosclerotic processes in the coronary vessels

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Table 1. Classification and factors influencing the development of in-stent restenosis

Type	Time Line	Factors from the patients	Factors from the lesion	Factors from the procedure
Acute	Within 24h	ACS-STEMI	Small vessel diameter	Residual dissection
Subacute	Within 30 days	Diabetes mellitus	Long lesion	Impropriate stent expansion
Late	After 30 days	Heart failure	Bifurcation lesion	Stent malposition
Very Late	After 1 year	Chronic kidney failure	CTO	Stents overlap
		Aging	Thrombosis	>30mm stents
		Smoking	Vein graft lesion	BMS/DES
		DAPT interruption		Stent design
		Malignancy		Drugs at the stent

ACS-STEMI-Acute Coronary Syndrome-ST Elevation Myocardial Infarction, CTO-Chronic Total Oclusion, BMS-Bare Metal Stent, DES-Drug Eluting Stent, DAPT Dual AntyPlateTherapy. Taken and adapter from(3).

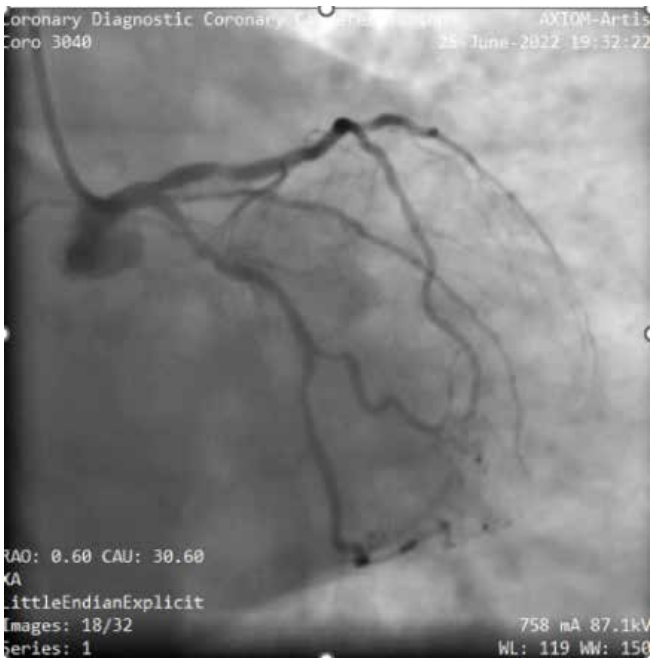


Figure 1a. Coronary angiography of the Cx (Circumflex artery) and LAD (Left Anterior Descending artery);

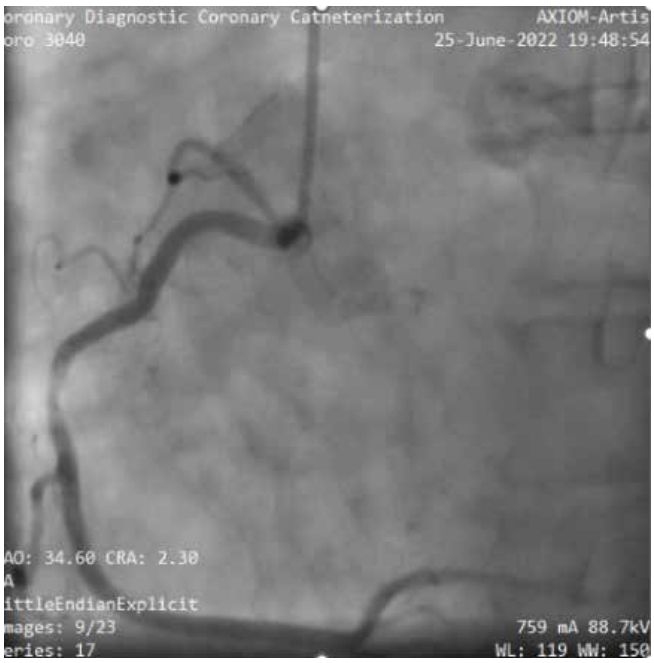


Figure 1b. Coronary angiography of the RCA (Right Coronary Artery).

and within the stent itself.Lesion-related factors include small vessel diameter, long lesions, bifurcation lesions, CTO (Chronic Total Occlusion), thrombosis, or lesions in vein graftsthat is, lesions requiring multiple stents; complex stent implantation procedures; the use of long stents or stents of smaller diameter, both of which are known to be more prone to thrombosis.Procedurerelated factors include inadequate stent positioning, overlap, or expansion; residual dissectionwhich is often unrecognized; the use of long stents; specific stent designs-especially oldergeneration devices with thicker struts; or the type of polymer and drug used in the stent (Table 1).

In recent years, intravascular imaging has become increasingly accessible and widely used, providing new informationnot only a quantitative assessment of the amount of tissue within the stent that partially or completely compromises blood flow, but also a qualitative assessment of the type of changes within the vessel or within the vessel wall, such as neointimal proliferation or neoatherosclerosis, with or without calcification[4].

Aim of the study

Presentation of case report which would highlight the important clinical dilemma of whether distinguishing neointimal proliferation from neoatherosclerosis as mechanisms of in-stent restenosis has significant therapeutic implications.

Case report

A 72-year-old female patient, D.Đ., was referred for rescue PCI after fibrinolysis for anterior-wall STEMI. On admission, signs and symptoms of heart failure were present. Her past medical history included chronic obstructive pulmonary disease, pulmonary sarcoidosis, and breast cancer. **Coronary angiography** showed suboclusive lesions in the Cx and LAD, as well as a significant lesion in the RCA (Figures 1a and 1b).

Given that this was a rescue PCI in the presence of heart failure, it was decided to treat the Cx and LAD. A Synergy 3×16mm stent at 12 atm was implanted in the Cx, and a Synergy 3.5×16mm at 10 atm in the LAD. The patient was on optimal medical therapy.

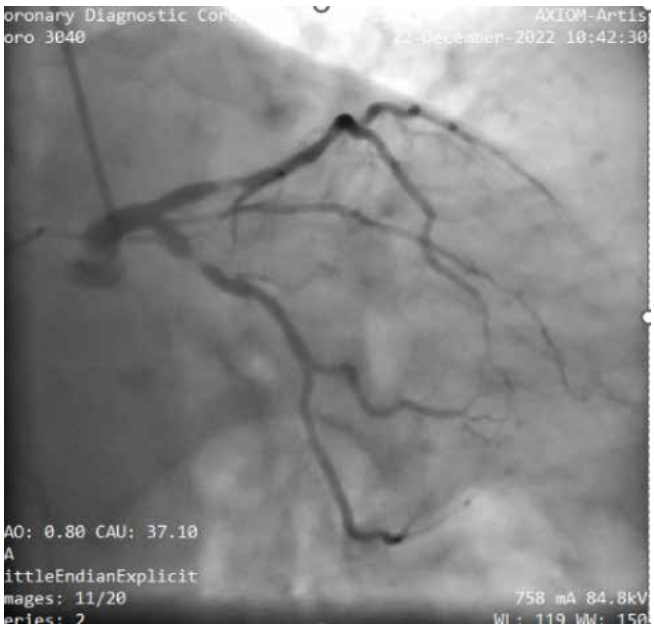


Figure 2. Coronary angiography showing in-stent restenosis of the Cx and LAD.

After six months, the patient was re hospitalized for anteriorwall NSTEMI. Coronary angiography revealed in-stent restenosis in the Cx and LAD (Figure 2). Both were treated with post-dilatation using an NC Mozec 3.5×18 balloon.

Four months later, the patient develops anginal pain again. Coronary angiography showed subocclusive restenosis in the Cx (Figure 3a). IVUS demonstrated calcium behind the stent and neointimal proliferation within the stent (Figure 3b). Because of the calcium behind the stentvisible on fluoroscopy during angiography-and inadequate stent expansion as a possible mechanism of restenosis, IVL was performed with a 3.5×15 balloon for 4 cycles. A DEB Elutax 3.5×20 was applied to the stent and proximal Cx for 55 seconds.

After eight months, another coronary angiography was performed due to chest pain and a positive exercise test. It revealed a subocclusive lesion in the Cx stent (Figure 4), which was treated with a 3.5×16 NC balloon.

Because of recurrent multiple in-stent restenosis, despite successful calcium removal by IVL and the presence of neointimal proliferation seen on IVUS, colchicine 0.5 mg daily was added for the next 12 months.

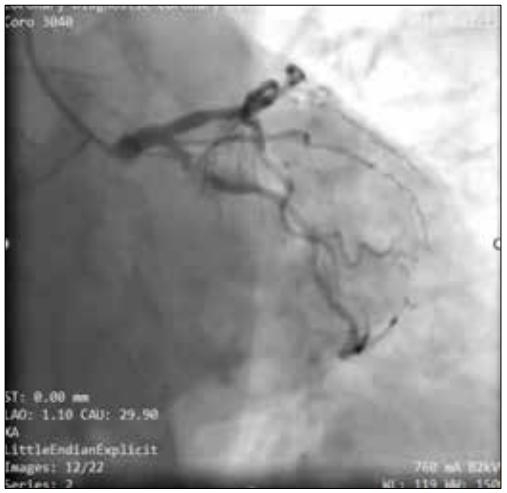


Figure 3a. Coronary angiography with in-stent restenosis in the Cx;

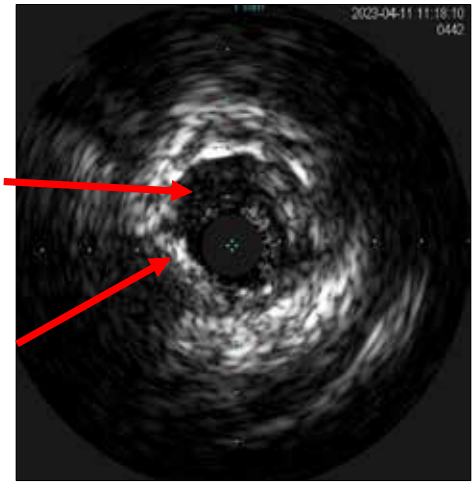


Figure 3b. IVUS demonstrating in-stent restenosis in the Cx (neointimal proliferation).

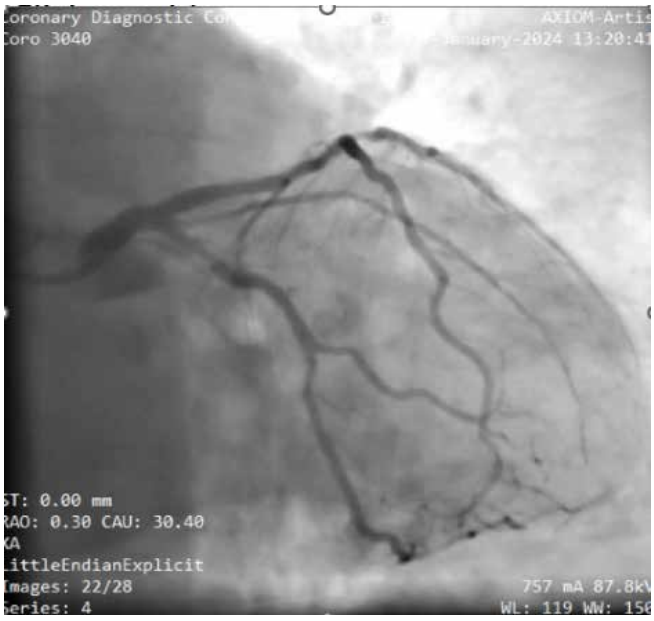


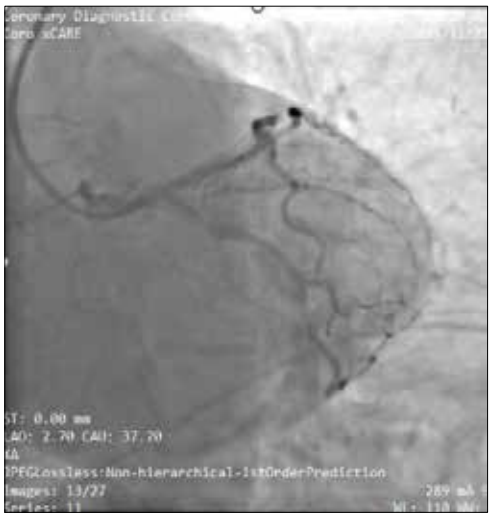
Figure 4. In-stent restenosis in the Cx.

After 12 months control coronary angiography again showed in-stent restenosis in the Cx (Figure 5a).

Repeat IVUS now demonstrated a small thrombus and areas of neoatherosclerosis as the mechanism of restenosis (Figure 5b). As there was no new neointimal proliferation, colchicine was discontinued. Due to the neoatherosclerotic changes, the instent stenosis was treated with repeat IVL using a 3.5×15 balloon for all 12 cycles and implantation of a new Synsiro 3.5×15 stent. Throughout treatment, the patient remained on optimal DAPT and intensive lipid-lowering therapy with rosuvastatin 40 mg and ezetimibe 10 mg, achieving adequate cholesterol control.

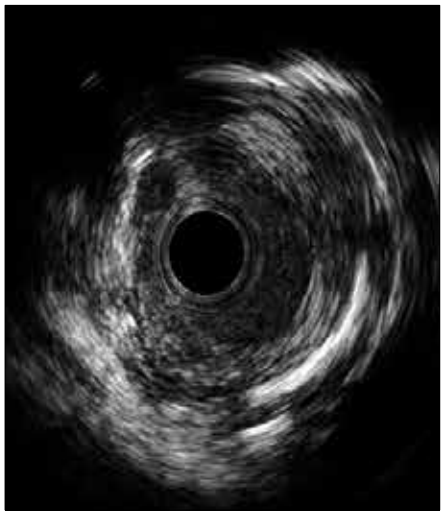
Discussion

Instent restenosis is rare but still present, even with new stent designs and modern drugeluting polymers. According to Waksman[5], mechanisms of in-stent resteno-



Thrombus

Figure 5a. In-stent restenosis in the Cx.



Neoateroclerosis

Figure 5b. IVUS showing restenosis due to neoatherosclerosis.

Table 2. Waksman In-Stent Restenosis Classification[5].

Type	Definition		Treatment Options
I	Mechanical	Underexpansion (Type I A)	High-pressure balloon
		Stent fracture (Type I B)	DES
II	Biologic	Intimal hyperplasia (Type II A)	Balloon, DEB, DES, and VBT
		Neoatherosclerosis, noncalcified (Type II B)	DCB and DES
		Neoatherosclerosis, calcified (Type II C)	Scoring balloon, ELCA, and RA
III	Mixed pattern: Combined mechanical and biologic etiology		High-pressure balloon with DEB, DES, or VBT
IV	Chronic total occlusion		DCB or DES, VBT for multiple layers, CABG as needed
V	>2 layers of stent		Balloon, DCB, VBT, and CABG

DES—drug-eluting stent; DEB—drug-eluting balloon; ELCA—excimer laser coronary atherectomy; RA—rotational atherectomy; VBT—vascular brachytherapy; CABG—coronary artery bypass graft.

sis may be mechanical (due to under expansion or stent fracture), biological (neointimal proliferation, neoatherosclerosis with or without calcification), combined (mechanical + biological), CTO, or involvement of more than two stent layers (Table 2).

When assessed along a timeline, **acute** (<24 h) and **subacute**(<1 month) restenoses almost always result from instent **thrombosis** due to malposition, underexpansion or stent fracture. These are typically resolved with balloon dilatation (Table 3).

However, in our experience, **late restenosis** (within 1 year) may be caused by neointimal proliferation or neoatherosclerosis. Treatment involves balloon dilatation followed by local drug delivery via DEB or placement of a new stent. The remaining question is whether this approach is appropriate in cases of neointimal proliferation. Pathophysiologicaly, **neointimal proliferation** results from endothelial cell dysfunction caused by stretching and pressure appliance during balloon dilatation and stent implantation. Endothelial activation triggers a cascade of mechanisms leading to proliferation:

1. Disturbed nitric oxide (NO) release in endothelial cells occurs within hours of mechanical stretch.

2. Platelet activation, contributing to instent thrombosis, also occurs within hours.

3. Inflammatory activation as a mechanism that occurs in the first days, leads to the activation of inflammatory cells.

Table 3. Types of in-stent restenosis, mechanisms of occurrence, and therapeutic options.

Type	Time Line	Mehanism	Therapy 1st Line	Therapy 2nd Line	Devices Therapy
Acute	Within 24h	Thrombosis	DAPT		Balloons (NC), DEB, DES
Subacute	Within 30 days	Thrombosis	DAPT		Balloons (NC), DEB, DES
Late	After 30 days	Neointimal proliferation	DAPT Statins	Colchicine MTx Sirolimus Paclitaxel	Balloons(NC, Scoreflex), DEB, DES, VBT
Very Late	After 1 year	Neoatherosclerosis	Statins		Balloons(NC, Scoreflex), DEB, DES, CABG

DAPT—Dual Antiplatelet Therapy; NC—Noncompliant; DEB—Drug-Eluting Balloon; DES—Drug-Eluting Stent; MTx—Methotrexate; VBT—Vascular Brachytherapy; CABG—Coronary Artery Bypass Graft.

Subsequent mechanisms that are activated and last for weeks and months lead to structural disorders in the thickness of the blood vessel wall.

4. Matrix metalloproteinase activation degrades elastin and collagen in the tunica media, enabling migration of smooth muscle cells into the intima[6]. There, smooth muscle cells transform phenotypically into secretory cells that producing mediators: growth factors, proteases, and inflammatory mediators, which drive neointimal proliferation.

According to Zain, neointimal proliferation may be *Arterial* as an endothelial response to endarterectomy or PCI, *Venous* as an endothelial response to CABG. After the first year, venous grafts undergo arterialization, and after year five, lumen reduction is primarily due to neoatherosclerosis[7].

Since the mechanism of neointimal proliferation is vesselwall stretch, the question arises whether additional balloon dilatation or new stent implantation is beneficial. Neointimal proliferation occurs within the first year, when DES still releases active cytostatic drug[8]. Therefore, local therapy via DEB plus systemic antiproliferative therapyoral or parenteralmay be preferable (Table 3). In the future, newgeneration bioresorbable scaffolds may play a role in first year fortreatment instent restenosis.

In our case, based on the COLCOT and LoDoCo2 trials and current guidelines[9], colchicine 0.5 mg daily was prescribed for 12 months. After one year, restenosis recurred but was identified by IVUS as neoatherosclerotic rather than neointimal. It remains unclear whether this systemic therapy effectively treats neointimal proliferation. Vascular brachytherapy is proposed as a lastline option (Table 3).

Very late restenosis (after 1 year) is caused by **neoatherosclerosis** the development of atherosclerotic changes within the neointima after stent implantation. It is characterized by inflammation, macrophages or foam cells phagocytosed lipids and cholesterol crystals. As with native atherosclerosis, a lipid pool is formed, in which a necrotic core usually appears[10]. The presence of a necrotic core is the basic substrate for calcium deposition, and it depends on whether neoatherosclerosis with calcification or without calcification will develop. Calcium in neoatherosclerosis is usually superficial and focal in the form of nodules, rarely deep and diffuse. In our case, IVUS demonstrated thrombus and neoatherosclerosis within the stent. This slow process develops over many years and can continue long term. It is treatable with balloon dilatation, local drug application (DEB), or repeat stenting (Table 3).

Conclusions

Instent restenosis, based on timing, may be acute, subacute, late, or very late. Its mechanisms include thrombosis, neointimal proliferation, and neoatherosclerosis. Regardless of timing, treatment involves balloon dilatation, use of DEB, or implantation of a DES. Only in cases of confirmed neointimal proliferation should additional therapy be consideredoral colchicine, methotrexate or sirolimus, or parenteral paclitaxel.

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Sažetak

In-stent restenoza: neointimalna proliferacija ili neoateroskleroza

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*In stent restenoza prema vremenu nastanka može biti: **Rana**-unutar 24, **Subakutna**-unutar prvog meseca, **Kasna**-unutar prve godine, **Veoma kasna**-posle prve godine. Bolesnica D.Đ., 72 godine stara upućena je na **spašavajuću PCI** (Percutaneus Coronary Intervention) nakon fibrinolize i STEMI prednjeg zida. Na koronarografiji viđene su subokluzivne lezije na Cx i LAD, kao i signifikantna lezija na RCA. Na Cx je plasiran stent Synergy 3x16 na 12 atm, na LAD Synergy 3,5x16 na 10 atm. **Nakon 6 meseci** nova hospitalizacija zbog NSTEMI (Non ST Elevation Myocardial Infarction) prednjeg zida. Urađena je rekoronarografija sa in stent restenozama na Cx i LAD koje su rešene postilatacijom balonom NC Mozec 3,5x18. **Nakon 4 meseci** ponovni bol u grudima, na koronarografiji suboklu-*

zivna restenoza u Cx. Na IVUS (IntraVascular Ultra Sound) vidi se prisustvo kalcijuma iza stenta i neointimalna prliferacija u stentu. Sproveden je IVL (Intra Vascular Lithotripsy) balonom 3,5x15 na 4 ciklusa. U stent i proksimalni deo Cx plasiran je DEB (Drug Eluting Baloon) Elutax 3,5x20 u trajanju od 55 sec. ***Nakon 8 meseci*** *ponovna koronarografija zbog bola u grudima i pozitivnog ergo testa. Na koronarografiji subokluzivna lezija u stentu u Cx koja ja rešena NC balonom 3,5x16. Zbog ponavljanih in stent restenoza i nakon uklanjanja kalcijuma uspešnim IVL, i prisutne neointimalne proliferacije, viđene na IVUS, u terapiju je uveden Colhicin 0,5mg dnevno, narednih godinu dana.* ***Nakon godinu dana****, na kontrolnoj koronarografiji viđena je ponovna in stent restenoza u Cx. Na ponovnom IVUS sada se uočava prisustvo manjeg tromba i zona neoakteoskleroze kao mehanizma in stent restenoze. Zbog neoaterosklerotičnih promena, in stent stenoza je tretirana ponovnim IVL balonom 3,5x15 svih svih 12 ciklusa, i implantacijom novog stenta Synsiro 3,5x15. In stent restenoza, u odnosu na vreme nastanka, može biti akutna, subakutna, kasna, veoma kasna. U odnosu na vreme nastanka, mehanizmi in stent restenoze mogu biti tromboza, neointimalna proliferacija i neoateroskleroza. Terapijski pristup je bez obzira na vreme nastanka je balon dilatacija, primena DEB ili DES. Jedino u slučaju dokazane neointimalne proliferacije razmotriti dodatnu per os primenu Colhicina, Metotrexata, Sirolimusa ili parenteralnu primenu Paclitaxela.*

Ključne reči: *In stent restenoza, tromboza, neointimalna proliferacija, neoateroskleroza.*