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Case report

Treatment challenges in a very high-risk diabetic patient with coronary artery disease

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Abstract We present 58-year woman with T2 diabetes mellitus and multiple cardiovascular risk factors who was addmited to our clinic due to unstabile angina. Coronary angiography revealed bifurcation lesion of medial left anterior descending coronary artery (LAD) with 90% stenosis and first diagonal branch (D1) with a vessel diameter of 2 mm, and percutaneous coronary intervention (PCI) with implantation of one drug eluting stent (DES) in medial LAD was performed. During the follow-up optimal blood pressure control was achieved with combination of antihypertensive drugs and poor glycaemic control was managed with adding empagliflosin to metformin. Trimetazidine was initiated as a second-line treatment to reduce angina symptoms. Repeated coronary angiography due to angina one year later showed patent stent in mid LAD, but gracile periphery of LAD and D1 branch, not suitable for PCI. Optimal medical tretment was indicated. Lifestyle changes were also recommended. Ezetimibe was added to statin therapy due to high levels of LDL cholesterol. Further multifactorial aproach and tighter control of risk factors is needed in order to prevent other vascular complications in this patient.

Kew words diabetes mellitus, acute coronary syndrome, unstabile angina, risk assesment, cardiovascular risk factors

Introduction

Diabetes mellitus (DM) increases the risk of coronary heart disease two times independent of other risk factors. Women and younger patients have higher relative risk of vascular events. Patients with long duration of DM and microvascular complications will have higher both relative and absolute risk levels[1].

Case presentation

We present an obese 58-year-old woman (body mass index 34 kg/m^2) who was admitted to our clinic in November 2018 due to crescendo angina. She has DM type 2 duration of 8 years on metformin therapy, hypertension, dyslipidemia diagnosed when she was 28 years old, positive family history of coronary artery disease (her father and uncle both had myocardial infarction at 42 years of age) and history of light smoking. The patient also has inflammatory myopathy and receives hormone therapy for hypothyroidism and inhalatory corticosteroids for asthma. Two weeks before admission she performed excercise electrocardiogram (ECG) because of suspected anginal symptoms, which showed low exercise tolerance and 2 mV ST-depression in leads DII, DIII, aVF, V3, V4, V5, V6 during rest.

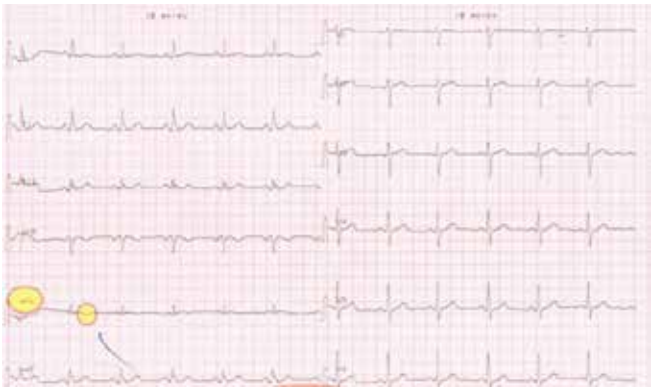

Figure 1. Resting electrocardiogram showed negative T wave in lead aVL.

On admission she was eupnoic, in sinus rhythm, heart rate 75 b.p.m, blood pressure was 130/80 mmHg and without clinical signs of heart failure (HF). Biochemistry testing showed normal values of high sensitive troponin I and creatin kinase (CK)-MB, with elevated values of CK (318 [26-200 U/l]), normal renal function and normal blood gas analyses. Resting ECG showed negative T wave in lead aVL (Figure 1). Transthoracic echocardiography (TTE) revealed normal left ventricle (LV) systolic function with no regional wall motion abnormalities. Invasive coronary angiography was performed and showed bifurcation lesion (Medina classification 0,1,1) of medial left anterior descending coronary artery (LAD) with 90% stenosis and first diagonal branch (D1) with a vessel diameter of 2 mm, 99% stenosis and muscular bridge in distal segment of D1

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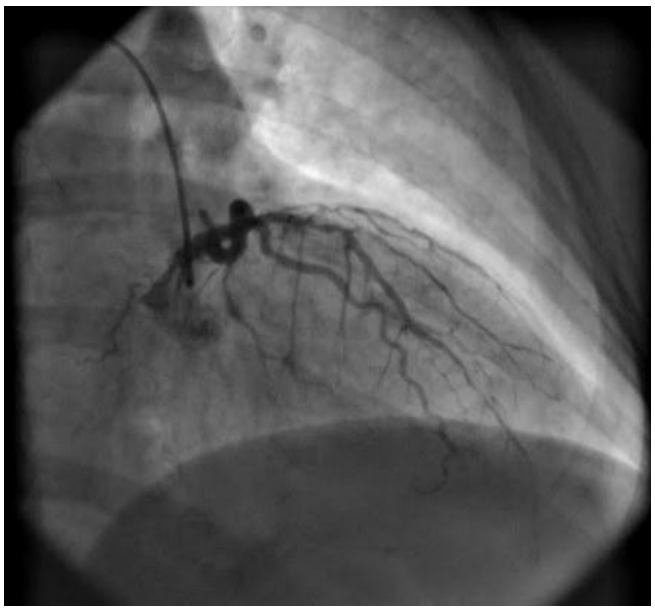

Figure 2. Bifurcation lesion of medial left anterior descending coronary artery (LAD) with 90% stenosis and first diagonal branch (D1) with a vessel diameter of 2 mm, 99% stenosis and muscular bridge in distal segment of D1

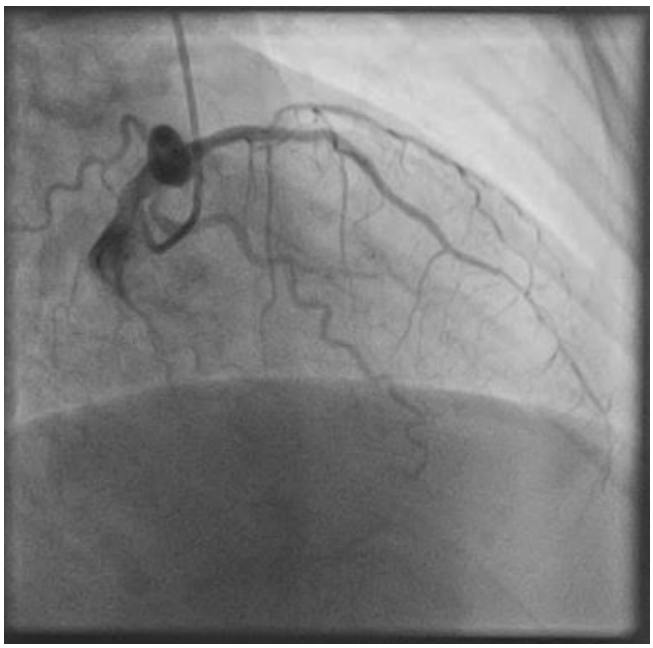

Figure 3. Repeated coronary angiography (Figure 3) showed patent stent in mid LAD, diameter of LAD peripherally <1.5 mm and narrow D1 branch with diameter ≤2 mm

(Figure 2A). Percutaneous coronary intervention (PCI) with implantation of one drug eluting stent (DES) in medial LAD was performed and followed by „POT-side-POT" with D1 branch (Figure 2B). TIMI 1 was achieved in D1 branch, although stent was not implanted because of narrow vessel diameter. The patient was discharged with dual antiplatelet therapy, bisoprolol 2,5 mg, perindopril 5 mg, rosuvastatin 20 mg, pantoprazol 40 mg and metformin 1000 mg b.i.d.

During the 6-months follow-up she was without ischaemic symptoms, however she experienced anginal symptoms again. Optimal blood pressure control was achieved by adding calcium channel blocker (amlodipin 5 mg) and thiazide-like diuretic (indapamid 1,25 mg). Statin dose was reduced (rosuvastatin 10 mg) due to increased levels of CK. In November 2019 the values of HbA1c were checked indicating poor glycemic control. Since HbA1 raised from 7.4 to 9.8% and the patient was considered as very high-risk, sodium-glucose co-transporter 2 inhibitor (SGLT2i) (empagliflozin 10 mg) was introduced into therapy. Excersise ECG revealed ST-depression in leads DII, DIII, aVF, V4, V5, V6 during rest. TTE showed preserved global systolic function, without wall motion abnormality. Repeated coronary angiography (Figure 3) showed patent stent in mid LAD. As part of negative remodeling, LAD periphery was gracile, diffusely atherosclerotic altered with vessel diameter <1.5 mm and narrow D1 branch with diameter ≤2 mm not suitable for PCI. Optimal medical tretment was indicated. Trimetazidine was initiated as a second-line treatment to reduce angina. Lifestyle changes were also recommended.

Three months after initiating SGLT2i therapy, control value of HbA1c is 8.2%. Considering persistent high LDL cholesterol (LDL-C) values (3.24 mmol/l), ezetimibe was added to therapy. Screening for microvascular complications of DM has been performed. Eye examination did not show signs of diabetic retinopathy, estimated glomerular filtration rate was 66 ml/min/1.73 m^2, microalbuminuria was not detected, and neurological investigation did not show signs of neuropathy. Value of ankle-brachial index (1,2 for right leg and 1,1 for left leg) and normal biphasic continuos wave Doppler curves excluded lower-extremity artery disease.

Discussion

Chest discomfort that meets criteria for crescendo angina (prior typical ischaemic symptoms escalate and appear at a lower threshold and over a short period of time) falls under the unstable angina which is managed according to the ESC guidelines for acute coronary syndromes (ACS)[2]. Glucose abnormalities are common both in patients with ACS or chronic coronary syndromes (CCS) and worsen the prognosis of these patients[3]. A meta-analysis including 5 324 patients with non-ST-segment elevation ACS and DM, an early invasive compared to delayed strategy showed reduced mortality at a median follow-up of 6 months (HR 0.67, 95% CI 0.450.99)[4]. Coronary revascularisation techniques should not differ among patients with and without DM (e.g. use of DES and radial approach for PCI). PCI is recommended for patients with DM and one- or two-vessel CAD without proximal LAD stenosis (class Ia) and has similar outcomes to CABG in diabetic patients with low complexity CAD (SYNTAX score ≤22)[5]. DM is already diagnosed in up to one third of patients with CAD and more than two third of patients with CAD have newly detected glucose abnormalities[6]. The values of HbA1c and fasting plasma glucose (FPG) are used to diagnose T2DM and when these values are inconclusive, oral glucose tolerance test (OGTT) is performed. In ACS

the OGTT should be done after four to five days, to minimize false-positive results[3,7].

According to the 2019 ESC Guidelines on Diabetes, Prediabetes and Cardiovascular Diseases (CVD) our diabetic patient was at very high-risk considering the fact she had DM with established cardiovascular disease and more than three major risk factors. The 10-year risk of CVD death for these patients is more than 10%. Female gender is also considered not to be protective for premature CVD in diabetes. Control of potentially modifiable risk factors to reach recommended targets is crucial for very high-risk diabetic patients. Lifestyle changes are cornerstone of prevention DM and its vascular complications and consider smoking cessation, reduction in calorie intake in order to reduce BMI, physical activity and a Mediterranen diet. Recommended value of blood pressure (systolic ≤130 mmHg, but not <120 mmHg and diastolic ≤80 mmHg, but not <70 mmHg) according to ESC guideline on Diabetes was achieved with combination of four group of antihypertensive drugs in our patient[3,8].

The recommended target values of HbA1c for patients with diabetes are <7% or <53 mmol/ml in order to reduce microvascular complications and the same values should be considered for preventing macrovascular complications[3]. In diabetic patients, FPG, post-prandial glycaemia and glucose variability were less strongly associated with CVD risk factors than HbA1c and mean blood glucose[9]. Although the role of glucose variability still needs to be defined, studies report that FPG variability is a strong predictor of all-cause and CVD-related mortality in individuals with DM[10]. Newer oral glucose-lowering drugs (glucagon-like peptide-1 receptor agonists (GLP1-RAs), dipeptidyl peptidase-4 (DPP4) inhibitors, and SGLT2i) reduce post-prandial glucose rise and might be appropriate tool for management of glucose variability[11]. Both GLP1-RAs and SGLT2i have also shown BP-lowering effects[12,13].

Data derived from several cardiovascular outcome trials recommend use of GLP1-RAs (liraglutide, semaglutide, or dulaglutide) and SGLT2 inhibitors (empagliflozin, canagliflozin, or dapagliflozin) in patients with T2DM who have atheroscrerotic CVD or high/very high CV risk, whether they already use metformin, like our patient, or are metformin naïve, as first line therapy (3). A meta-analysis of three trials (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58) with SGLT2 inhibitors showed reduced composite of HF hospitalisation or CV death, reduced progression of kidney disease (regardless of atheroscrerotic CVD presence) and reduction of MACE in individuals with established CVD[14]. The CREDENCE trial[15] with canagliflosin compared to placebo showed relative reduction of the primary renal outcome of 30% in patients with T2DM and albuminuric chronic kidney disease. Favorable results in these trials are probably due to reduction in HF-associated events and can be explained with impact of SGLT2i on hemodynamic parameters (e.g. reduced plasma volume)[16]. American Diabetes Association still prefers metformin as initial pharmacologic agent for the treatment of T2DM and the second medication added to metformin is based on the clinical characteristics of the patient (e.g. established ASCVD or indicators of high ASCVD risk)[17].

Statin therapy is first-line lipid-lowering treatment and if the target LDL-C is not achieved, addition of ezetimibe is recommended[18,19]. Our patient received reduced dose of rosuvastatin, which is considered to has a lower rate of side effects[20]. In patients on maximal tolerated dosages of statin therapy, when LDL-C was above 1.8 mmol/L, addition of proprotein convertase subtilisin/kexin type 9 (PCSK9) additionaly lowered the LDL-C. This result showed the strength of PCSK9 compared to statin therapy. Reduction of LDL-C led to lowering the incidence of CV endpoints, especially in those patients who had LDL-C >2.6 mmol/l. Therefore lowering of LDL-C after acute coronary syndrome from previously suggested 1.8 mmol/l to 1.4 mmol/l is now recommended[21]. In very high-risk patients, with persistent high LDL-C despite treatment with a maximum tolerated statin dose, in combination with ezetimibe, or in patients with statin intolerance, a PCSK9 inhibitor is recommended to target an LDL-C of <1.4 mmol/L (<55 mg/dL) or at least 50% LDL-C reduction[3].

Further multifactorial aproach and tighter control of risk factors is needed in order to prevent microvascular and other macrovascular complications in this patient.

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Sažetak

Prikaz slučaja: Izazovi u lečenju veoma visoko rizičnog pacijenta sa dijabetes melitusom i koronarnom arterijskom bolešću

Žena starosti 58 godina sa T2 dijabetes melitusom i mnogobrojnim kardiovaskularnim faktorima rizika je primljena na našu kliniku zbog nestabilne angine. Urađena je koronarografija kojom se registruje bifurkaciona lezija 90% sužene prednje silazne koronarne arterije (LAD) i prve dijagonalne grane (D1) sa dijametrom krvnog suda 2mm, i u istom aktu perkutana koronarna intervencija (PCI) sa implantacijom jednog lekom obloženog stenta u medijalni segment LAD. Tokom daljeg praćenja je kontrola krvnog pritiska postignuta kombinacijom antihipertenzivnih lekova, dok je loša glikemijska kontrola tretirana dodavanjem empagliflozina metforminu. Trimetazidin je uveden u terapiju kao druga linija antianginoznih lekova. Ponovljena je koronarografija godinu dana kasnije zbog anginozih tegoba i registrovan je prohodan stent u LAD i gracilna periferija LAD i D1, nepogodna za PCI. Indikovan je optimalni medikamentni tretman. Preporučene su promene životnih navika. Ezetimib je dodat statinskoj terapiji zbog povišenih vrednosti LDL holesterola. Neophodan je nastavak multidisciplinarnog lečenja i stroža kontrola faktora rizika kako bi se prevenirale dalje vaskularne komplikacije kod ove pacijentkinje.

Ključne reči: *dijabetes melitus, akutni koronarni sindrom, nestabilna angina, procena rizika, kardiovaskularni faktori rizika*