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Particularities of multivessel disease in a diabetic patient

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Abstract

Atherosclerosis is a complex chronic inflammation in the large and medium arteries that is most often associated with hyperlipidemia and/or several other risk factors. Diabetes mellitus has also been shown to dramatically influence the extent and clinical complications of atherosclerosis, moreover, patients with diabetes are known to have a predisposition to develop multivessel disease. We report a case of resistant hypertension associated with multivessel disease in a diabetic patient. The presence of progressive kidney failure, initially interpreted in the context of diabetic nephropathy and found to be due to severe renal artery stenosis, and the presence of atherosclerotic disease in the previously discovered cerebral and coronary arteries and in the recently found carotid and renal artery territories, without affecting the peripheral arteries and rather unexpected in a diabetic smoker, represent particularities of this clinical case.

Keywords: multivessel disease, atherosclerosis, resistant hypertension, diabetes mellitus, kidney artery stenosis

INTRODUCTION

Atherosclerosis, a pathology that was proven to be due to chronic inflammation of the arteries, with predilection in the vessels with non-laminar flow and bifurcations (1), is still a major cause of high mortality and morbidity in the world population (2). Multivessel disease, as a consequence of systematic atherosclerosis of the coronary arteries (two or more coronary arteries with diameter >= 2.5 mm) (3), also represents a major mortality cause worldwide and is associated with a high rate of STEMI infarctions (4). Renal arteries can also be affected by atherosclerotic plaques leading to atherosclerotic renal artery stenosis, followed by an increase in secondary renovascular hypertension, which further aggravates the outcome of the underlying cardiovascular disease (5). Diabetes mellitus (DM), as a condition associated with micro and macrovascular complications, associates a very high risk for coronary artery disease (CAD) occurrence. Furthermore, in a study by Haffner et al., patients with DM and CAD without myocardial infarction have an equal risk for developing myocardial infarction as CAD patients with previous myocardial infarction and therefore cardiovascular risk management and primary prevention treatment should be assessed in these patients with no delay (6). Burgess et al. also studied the impact on cardiovascular mortality for patients who associated both multivessel disease and DM and suffered STEMI infarctions. Their results highlighted the high cardiac mortality in diabetic vs. non-diabetic patients with STEMI and multivessel disease (7). In the light of these findings, we present a

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case of a diabetic patient that despite of having complex atherosclerosis affecting multiple arterial systems such as coronary, cerebral (sylvian territory), carotid and renal arteries, and having more underlying high cardiovascular risk conditions such as hypertension, dyslipidemia and a smoking habit, did not associate peripheral arterial disease.

CASE PRESENTATION

A 73-years-old male with a history of essential hypertension grade 3 and coronary heart disease (CHD) presented in our clinic with insufficiently controlled blood pressure (BP) values, dyspnea on light exertion and fatigue. CHD was previously diagnosed following anterior ST-elevation myocardial infarction (STEMI) for which percutaneous transluminal coronary angioplasty (PTCA) with Multi Link 2.5/18 mm stenting of left anterior descending artery (LAD) was performed in 2014. Prior to this condition he suffered a right sylvian artery stroke in 2010 and was known to suffer from type 2 diabetes mellitus since 2001. The patient also had a plethora of cardiovascular risk factors besides age, gender, hypertension and diabetes mellitus, being an active smoker for 25 years (600 pack/year) diagnosed with chronic obstructive pulmonary disease (COPD) and atherogenic dyslipidemia. His current medications included budesonide/formoterol fumarate dehydrate 160/4.5 mcg inhaled twice daily, metformin 1000 mg bid daily, bisoprolol 2.5 mg once daily, ramipril 10 mg once daily, amlodipinum 5 mg once daily, furosemide 40 mg once daily, clopidogrel 75 mg once daily, aspirin 100 mg once daily and rosuvastatin 10 mg one daily.

On physical examination the patient was overweight with a body mass index = 29.02 kg/m2, had slightly increased bilateral basal vesicular sounds, without added crackles, peripheral O_2 saturation (SpO_2) of 95% while breathing room air, blood pressure (BP) = 170/95 mmHg, a heart rate (HR) of 64 beats/min and a systolic regurgitant murmur in the mitral area.

Laboratory test results found to be pathological are shown in Table 1.

TABLE 1. *Pathological values of the laboratory test performed at admission*

Laboratory test	Conventional units	Value	Reference range value
Hemoglobin	g/dl	11.7	12.4-16.1
Hematocrit	%	34	35.4-46.3
Glycosylated hemoglobin (HbA1c)	%	7.3	4-6
Blood glucose	mg/dl	170	74-106
Creatinine	mg/dl	1.82	0.55-1.02
LDL-cholesterol	mg/ml	76	≤ 100
Microalbuminuria	mg/day	300	≤ 30

The electrocardiogram (ECG) showed regular sinus rhythm, HR = 61 beats/min, QRS axis deviated to the left, poor R wave progression in V1-V3, without acute ischemic changes (Figure 1).

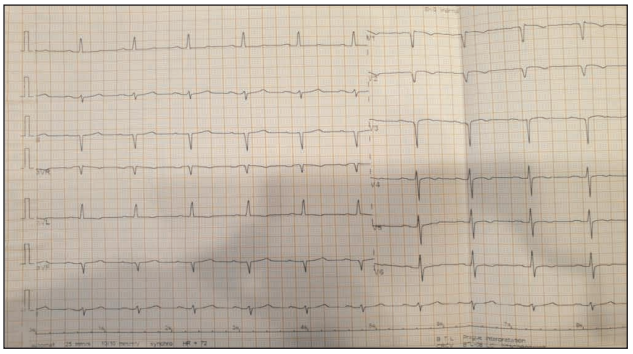

FIGURE 1. *ECG performed on admission*

The chest X-ray performed on admission showed cardiomegaly, prominent aortic knob, increased vascular density in the upper half of both hila and diffuse pulmonary emphysema (Figure 2).

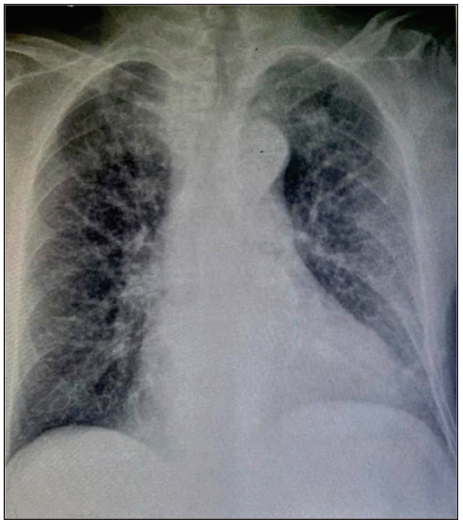

FIGURE 2. *Chest X-ray of the patient performed on admission*

During hospitalization in our clinic the patient underwent an Ambulatory Blood Pressure Monitoring (ABPM). The monitoring was made between 11.30 AM and 11.30 AM with measurements at intervals of 20 minutes during the day and at 30 minutes at night. The success index of the measurements was 94%. The mean arterial blood pressure for 24 hours was 141/83 mmHg. The dipping index was 8.90%, showing a non-dipper profile with mild nocturnal hypertension (mean nocturnal BP = 133/77 mmHg compared to the upper limit of normal 120/70 mmHg) (Figure 3).

The ankle-brachial index (ABI) test on the right side was 0.9 and on the left side was 1.2 (normal values between 0.9 and 1.3). The carotid Doppler ultrasonography showed a left common carotid artery (LCCA) fol-

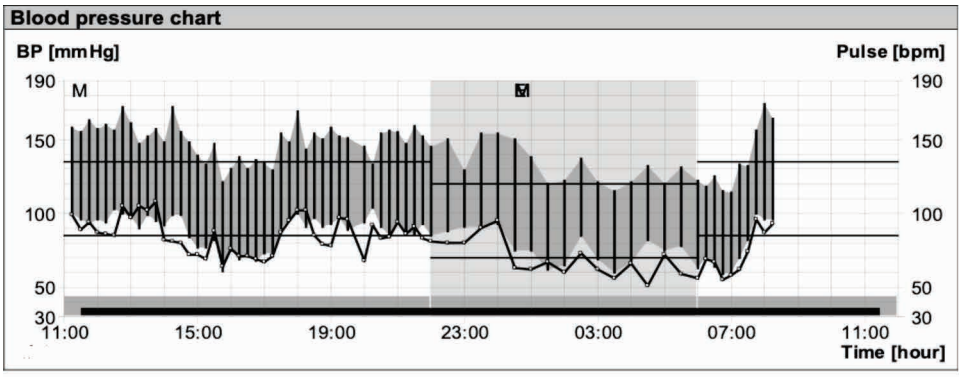

FIGURE 3. *The ABPM performed showing a non-dipper profile*

lowing a rectilinear path and intima media-thickness (IMT) = 1.1 m (normal values < 0.9 mm), while the left internal carotid artery (LICA) presented a calcified plaque with 75% stenosis. The right common carotid artery (RCCA) also followed a rectilinear path and IMT = 1 mm, without significant plaques or stenosis (Figure 4).

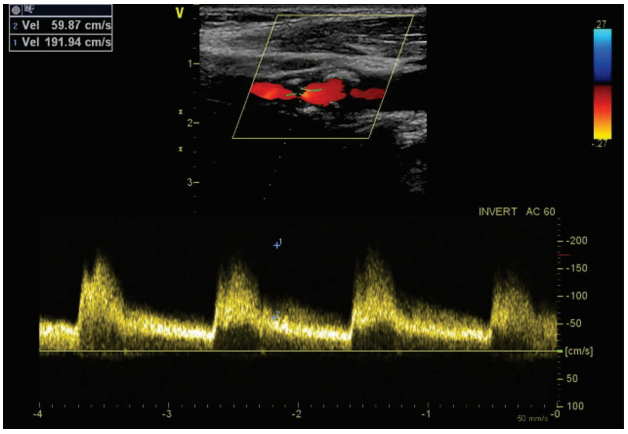

FIGURE 4. *The carotid Doppler ultrasonography of the left ICA*

On transthoracic echocardiography calcifications of the aortic ring and mitral ring were observed, with a dilated ascending aorta (4.5 cm) and left atrial enlargement (5.1 cm). Also concentric left ventricular hypertrophy, left ventricular (LV) diastolic dysfunction type 1 and degenerative mitral regurgitation grade I were present. The planimetric ejection fraction was intermediate 48%, and a hypokinesia of the anterior wall, apex and interventricular septum (IVS) were noted (Figure 5).

Two dimensional speckle tracking echocardiography (2D-STE) that analysed global left ventricular strain (GLS) revealed a value of -7.7%, significantly decreased in the antero-septal segments (Figure 6).

A control angio-coronarography was performed and revealed a left main coronary artery without significant lesions, patent stent in the mid-segment of the left anterior descending artery (LAD), 40% proximal stenosis of the I diagonal, 30% stenosis of the intermediate coronary artery, 40-50% ostial stenosis of the left circumflex artery (LCX) and insignificant serial stenosis of the right coronary artery (RCA) (Figure7).

On abdominal ultrasound hepatic steatosis and a small left kidney of 66/38 mm were found, while the right kidney had normal dimensions (128/54 mm), without urolithiasis or hydronephrosis. This finding was consistent with suspected renal artery stenosis that could explain the failure to control hypertension with 3 doses of antihypertensive drugs and also the sudden deterioration of renal function, while the patient was following an angiotensin converting enzyme inhibitor (ACEI) regimen. As a next step of investigation, the patient underwent abdominal and peripheral arterial

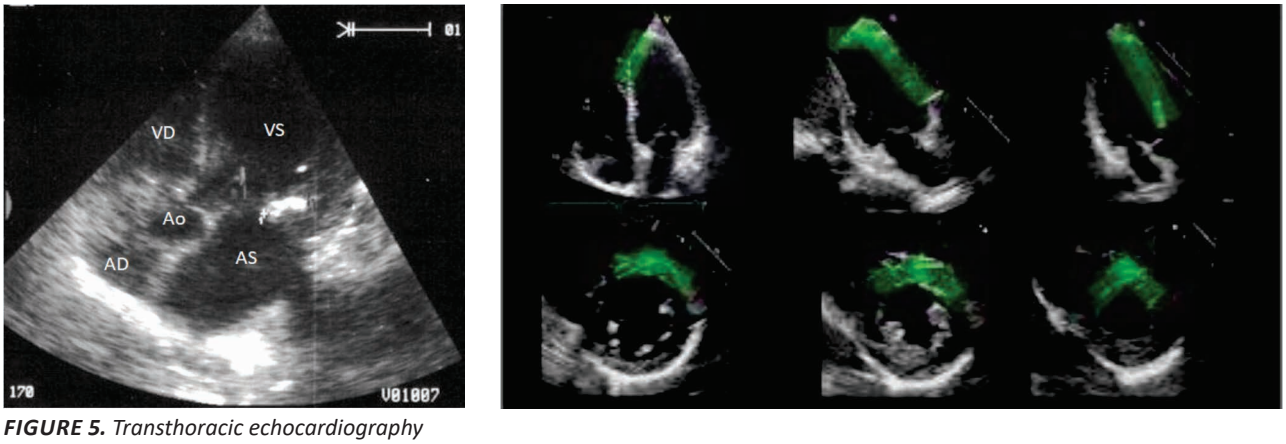

FIGURE 5. *Transthoracic echocardiography*

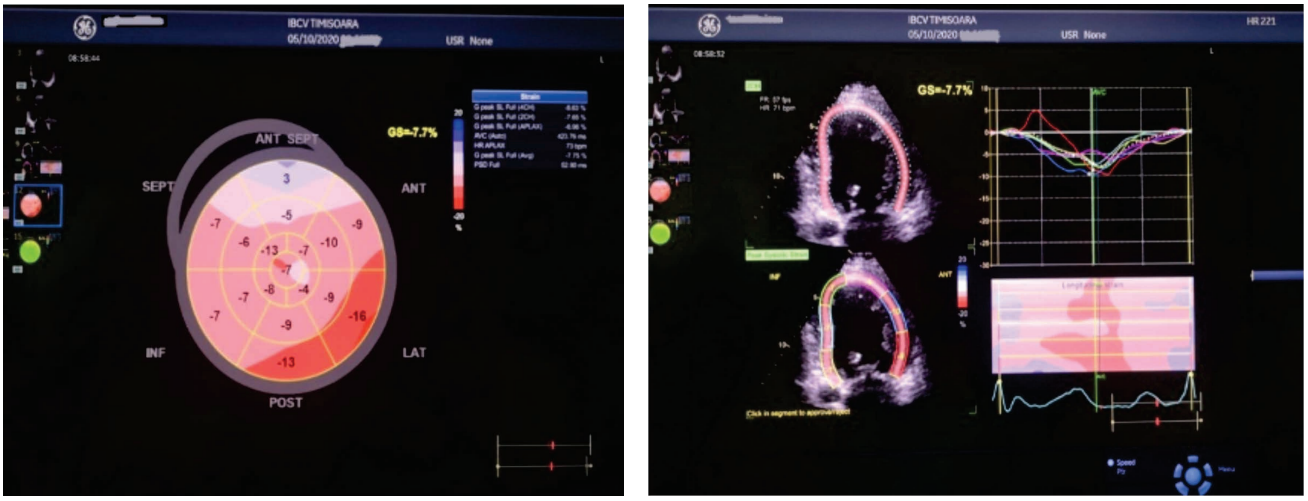

FIGURE 6. *2D-speckle tracking echocardiography with GLS = -7.7%*

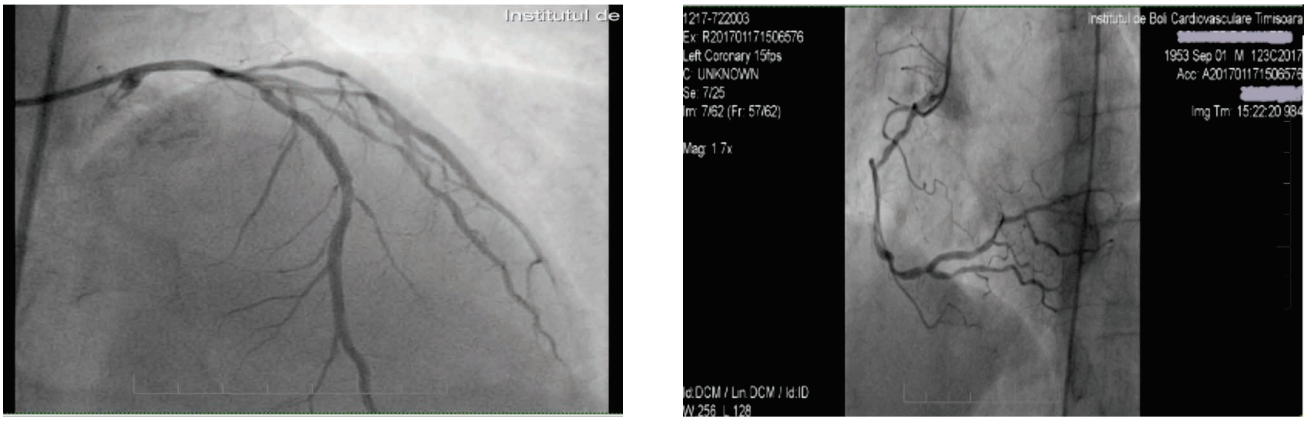

FIGURE 7. *Control angio-coronarography*

computed tomography angiography that revealed an abdominal aorta with small atherosclerotic plaques and circumferential peripheral calcifications, without dilatation or aneurysmal dissection. Calcareous atheromatosis at the origin of the left renal artery, small cortical cysts and delayed secretion in the left kidney were found. The appearance suggested severe chronic stenosis of the left renal artery. The anterior branches protruding from the abdominal aorta were permeable. Both common and superficial iliac arteries were permeable with normal appearance. The bilateral superficial femoral and popliteal arteries and their trifurcations were normal (Figure 8).

The positive diagnostic was reformulated to include all vascular territories affected: severe chronic stenosis of the left renal artery with grade 3 secondary reno-vascular hypertension and very high additional risk; bivascular coronary artery disease (LAD, LCX); ectatic ascending aorta; ischemic dilative cardiomyopathy; NYHA II heart failure with moderate ejection fraction (EF = 48%); right sylvian artery stroke; left internal carotid artery stenosis; type 2 diabetes mellitus; chronic kidney disease stage G3B A2 KDIGO; chronic obstructive pulmonary disease GOLD 2.

Based on the results of investigations performed during hospitalization, new associations of antidiabetic and antihypertensive medications were prescribed in accordance to present-day guidelines: sitagliptin 100 mg daily and dapagliflozin 10 mg daily for diabetes control in a patient who associates chronic kidney disease and heart failure, gradual up-titration to daily single doses of 10 mg amlodipine and 5 mg bisoprolol, along with moxonidine 0.4 mg daily to attain the BP target of < 130/80 mmHg. The daily dose of 40 mg furosemide to control fluid retention in heart failure was kept, also keeping the same regimen of double antiplatelet therapy because of multivessel disease, while increasing rosuvastatin to 20 mg daily to reach the recommended LDL target of < 55 mg/dl. All these were doubled by strict lifestyle recommendations which included weight loss, daily 30 minute walks, a heart-friendly diet and quitting smoking.

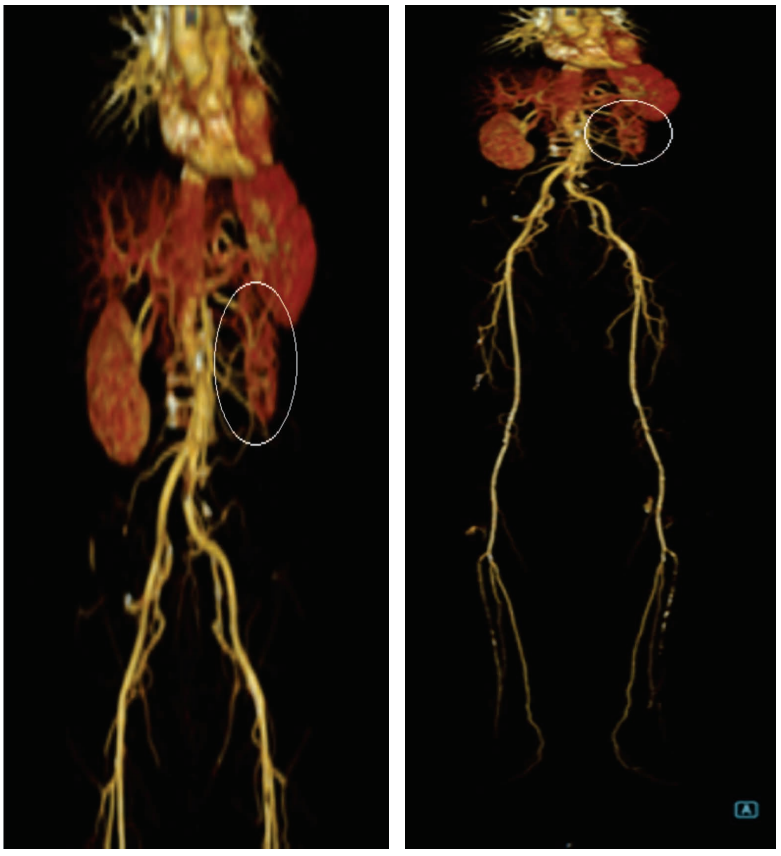

FIGURE 8. *Abdominal and peripheral CT angiography showing the small left kidney*

DISCUSSIONS

This was a patient with long-standing hypertension and diabetes, in whom already two different locations of atherosclerotic disease were known to be present when he addressed our service: cerebral and coronary. At first, his complaints only seemed connected to the evolution of ischemia and consecutive heart failure and suspected lack of compliance to medication with skipping doses, which is a frequent situation in clinical practice. His progressive kidney failure was also initially interpreted in the context of diabetic nephropathy, especially because of the association with microalbuminuria. However, further investigations changed this picture, because of the discovery of a small kidney, which turned out to be due to severe renal artery stenosis. This particularity did explain the lack of response to treatment of his hypertension.

The control of resistant hypertension is a challenge for clinical practice. The pathophysiological interactions between the sympathetic nervous system, impaired vasoreactivity, microvascular dysfunction and vascular remodeling which occur by the associated effects of diabetes and renal stenosis are complex and have to be addressed by a careful choice of medications.

Moxonidine, a centrally acting selective agonist at imidazoline I_1 receptors, was chosen for treatment of this patient (8). Moxonidine inhibits peripheral sympathetic activity, which decreases peripheral vascular resistance without reflex tachycardia accompanied by significant decreases in systolic and diastolic blood pressure. Also, moxonidine has minimal effect on cardiac hemodynamics and reduces left ventricular mass (9). Considering its efficacy, safety and specific effects (e.g., its ability to reduce left ventricular hypertrophy), moxonidine meets the criteria required by other currently prescribed antihypertensive drugs (10). Markers of endothelial dysfunction and end-organ damage, including microalbuminuria, improved in hypertensive patients who achieved BP control with moxonidine. Moxonidine also improved the metabolic profile of patients with hypertension and type 2 diabetes or impaired glucose tolerance (9). Also, a 3-year trial conducted by Littlewood et al. showed that treatment with standard antihypertensive therapy and adjunctive moxonidine in patients with advanced renal failure was predicted to reduce the number of new end-stage renal disease cases compared to adjunctive nitrendipine. The model showed that adjunctive moxonidine seems to increase life-years lived (11). This was the rationale for choosing it in this patient.

Despite more than 30 years of clinical trials, uncertainty still exists regarding the optimal use of antihypertensive drugs in patients with coronary artery disease (12,13). The comparison of amlodipine vs. enalapril to limit occurrences of thrombosis (CAMELOT) study compared treatments using either of 2 classes of antihypertensive drugs, a calcium channel blocker (amlodipine) and an ACEI (enalapril), with placebo in normotensive patients with CAD. In patients with CAD treated with a "standard of care" regimen including high doses of statin and aspirin, addition of amlodipine for 24 months resulted in a 31% relative reduction and a 5.6% absolute reduction in adverse cardiovascular outcomes (14). In the ASCOT-CAFÉ trial, amlodipine was more efficient than atenolol in reducing the systolic arterial pressure in the central aorta, an effect that is needed in this patient because of the presence of aortic ectasia (15).

We preferred the association between amlodipine and moxonidine to control blood pressure, renouncing the previous ACEI with ramipril, which could have further deleterious effects of worsening chronic kidney disease. For a better anti-ischemic effect, we increased the dose of beta-blocker and amlodipine, according to the 2018 ESC guidelines for chronic coronary syndromes.

For diabetic control, metformin had to be replaced with sitagliptin, up-titrated from 50 to 100 mg, because of the presence of chronic kidney disease. Dapagliflozin was added because the glomerular filtration rate (GFR) of 36.9 ml/min/1.73 m^2 allowed this choice and this medication proved to be beneficial vs. placebo in reducing cardio-vascular deaths and heart failure events in recent trials, in patients with heart failure with low ejection fraction (16).

Another particularity of this case is the fact that in spite of multiple locations of atherosclerotic disease, in the previous cerebral and coronary and the newly-found carotid and renal artery teritories, it did not affect peripheral arteries, all the more unexpected in a diabetic smoker. This could only partially be explained by the physiotherapy procedures that the patient claims to address regularly.

Regarding further interventions, the patient has underwent a percutaneous transluminal coronary angioplasty (PTCA) with the placement of a XACT 6-8/40 mm stent in his left internal carotid artery. For the renal artery stenosis further investigation of the functionality of the left kidney, the opportunity of stenting or even nephrectomy will be considered in time. Blood pressure control and improvement of kidney function under the new treatment will be closely monitored.

CONCLUSIONS

The complexity of this case is nevertheless regarding the association of high cardiovascular risk pathologies, such as hypertension and diabetes mellitus with a poor medication management in a patient who already associated coronary artery disease and suffered a stroke. Perhaps systematic investigation of all possible atherosclerosis sites and secondary prevention treatment should have been conducted earlier in this case in order to prevent treatment-resistant renovascular hypertension and kidney failure. However, the lack of treatment compliance combined with absolutely no lifestyle changes increase the risk for further atherosclerotic complications, which further lead to a higher disability and mortality. Also, kidney failure in a diabetic patient should be investigated more extensively due to the high risk of renal artery stenosis secondary to atherosclerotic plaques.

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