Advanced coronary artery disease in systemic lupus erythematosus – a case report and brief review of literature

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Abstract: **Background –** Systemic lupus erythematosus (SLE) affects young women, in smaller degree young men. Particularly male SLE phenotype presents poor prognosis and miscellaneous organ damage. Subsequent SLE atherosclerosis along with unremarkable traditional atherogenic risk factors determines severe coronary artery disease (CAD) in long-standing SLE disease. The clinical profile, diagnostic and management algorithm are considered, as well as a brief review of current literature. **Case presentation –** A 66-year-old Caucasian male with SLE diagnosed in 1998 was admitted for extended cardiovascular assessment. Due to severe pancytopenia related to SLE targeted therapy, the patient was placed on a time-adjusted dosage of corticosteroids. Thorough the time, patient developed dilated cardiomyopathy, atrial fibrillation (AF) and progressive heart failure (HF), in the absence of a close cardiac follow-up. Coronary angiography revealed severe coronary artery disease without evidence of marked atherogenic risk factors. However, the patient experienced non-traditional atherosclerotic risk factors such as hyperhomocysteinemia (HH), increased oxidized low-density lipoprotein cholesterol (OxLDL), and hyperphosphatemia. **Conclusion –** Cardiac involvement is a frequent manifestation of SLE, associated with a high morbimortality. Management of CAD, AF and HF with mild reduced ejection fraction (HFmrEF) in a SLE patient with severe chronic kidney disease (CKD) is challenging. An individualized strategy of close follow-up in nonorgan-specific auto-immune disease patients is needed.
Keywords: systemic lupus erythematosus, coronary artery disease, heart failure, hyperhomocysteinemia, oxidized low-density lipoprotein cholesterol.

Rezumat: **Introducere –** Lupusul eritematos sistemic (LES) afectează femeile tinere şi într-o mai mică măsură, pacienţii tineri de sex masculin. Fenotipul masculin al LES este deosebit, prezentând un prognostic negativ şi afectare organică multiplă. Ateroscleroza determinată de LES, alături de factorii de risc aterogenici tradiţionali, determină boală coronariană severă la pacienţii vârstnici. Sunt prezentate profilul clinic, diagnosticul şi algoritmul de management, alături de o scurtă trecere în revistă a literaturii actuale. **Prezentarea cazului –** Un bărbat caucazian în vârstă de 66 de ani, diagnosticat cu LES în 1998 a fost internat pentru evaluare cardiovasculară extinsă. Datorită pancitopeniei severe secundare terapiei specifice LES, pacientul a fost tratat cu corticosteroizi, doze ajustate în timp. Pacientul a dezvoltat cardiomiopatie dilatativă, fibrilaţie atrială şi insuficienţă cardiacă progresivă, fără monitorizare cardiologică constantă. Coronarografia a evidenţiat o afectare coronariană multivasculară severă, în absenţa unor factori de risc aterogenetici tradiţionali notabili, pacientul prezentând factori de risc aterosclerotic neconvenţionali: hiperhomocisteinemia, lipoproteine oxidate cu densitate mică, hiperfosfatemie. **Concluzii –** Afectarea cardiacă este o manifestare semnificativă în LES, asociată cu o morbiditate şi mortalitate ridicată. Managementul bolii coronariene în prezenţa fibrilaţiei atriale şi a insuficienţei cardiace cu fracţie de ejecţie moderat redusă la un pacient cu LES reprezintă o provocare. Este necesară o strategie individualizată de urmărire atentă a pacienţilor cu boli autoimune non-organ specifice.
Cuvinte cheie: lupus eritematos sistemic, boală coronariană, insuficienţă cardiacă, hiperhomocisteinemie, lipoproteine oxidate cu densitate mică.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex chronic autoimmune inflammatory disorder that mainly affects young women, and to a smaller degree, young men as well. In elderly SLE patients with long-standing disease, coronary artery disease (CAD) was confirmed as a common cause of mortality[1,2]. Male SLE patients display particular features, have a worse prognosis and multiple organ damage[3]. Furthermore, SLE patients have an up-to 3.39 increased risk for cardiovascular disease (CVD) compared to non-SLE individuals, particularly young women[4,5].

The non-traditional SLE risk factors for CVD, distinctively secondary to atherosclerosis surpass the traditional atherosclerotic risk factors. Dyslipidaemia is commonly linked to corticosteroid treatment[1].

Specific SLE dysregulated immune responses are associated with both increased risk of premature atherosclerotic plaques development along with an increased risk of plaque rupture. Consequently, luminal thrombosis, plaque erosions, and calcified nodules have a high risk of occurrence, thus triggering acute coronary syndrome (ACS). Coronary arteritis and thrombosis related to coronary aneurysms or antiphospholipid syndrome can also lead to ACS[6].

Kidneys are affected in about 50% SLE patients, with a higher risk of hyperhomocysteinemia and increased serum phosphate levels[7]. In particular, patients with lupus nephritis (LN) express remarkable incremental CV mortality compared to non-LN SLE patients[8].

CASE PRESENTATION

A 66-year-old Caucasian male with long-standing SLE (diagnosed in 1998, met SLICC criteria in 2012) was admitted in an university-based hospital for extended cardiovascular assessment.

Lupus nephritis, CKD and secondary hypertension were diagnosed in 2004. A percutaneous renal biopsy was never performed; therefore, the classification of LN accordingly to "The 2003 International Society of Nephrology/Renal Pathology Society classification of LN" was inapplicable[9].

Severe pancytopenia related to administration of antimalarial agents (Hydroxychloroquine) or immunosuppressive (Methotrexate or Azathioprine) was documented. Due to disease activity and despite emergent side-effects of long-term corticotherapy, Prednisone was prescribed, time-adjusted dosage, starting with 70 mg daily in 2004, down-titrated to 10 mg (from 2005). In February 2018 patient's SLEDAI-2K (SLE Disease

Activity Index) score was 32, as a consequence of significant organ involvement after a long evolution of the disease: visual disturbances, arthritis, urinary casts, hematuria, pyuria, rash, and alopecia (Figure 1).

Markers for secondary hyperparathyroidism and renal osteodystrophy were present: increased serum phosphate levels, elevated intact parathormone serum levels, and reduced 1.25-dihydroxy vitamin D.

With inconstant CV follow-up, in 2017 ischemic dilated cardiomyopathy, mitral regurgitation (MR), AF, HFmrEF NYHA functional class III, and severe CKD were diagnosed.

Dyslipidaemia status was unremarkable throughout disease evolution (Figure 2).

On admission, physical examination revealed moon face, moderate pitting edema. An irregular cardiac rhythm (heart rate: 100 bpm, peripheral pulse: 80 bpm), mild MR murmur, left anterior tibial peripheral pulse absence were found. A diminished bilateral pedal pulse was present.

Laboratory tests showed mild anemia, NT-proBNP value of 32,604 pg/mL (normal values <210.0 pg/mL), positive ANA antibodies (1:320, normal range <1:40), a homogenous pattern and normal titres for anti-dsDNA Ab, anti Smith Ab, anti SSA Ab, anti SSB Ab, anti RNP 70 Ab, anti ribosomal P protein Ab, anticardiolipin Ab, anti phospholipid Ab (Ab against beta 2-glyco-protein I, cardiolipin, phosphatidylinositol, phosphatidylserine, phosphatidic acid).
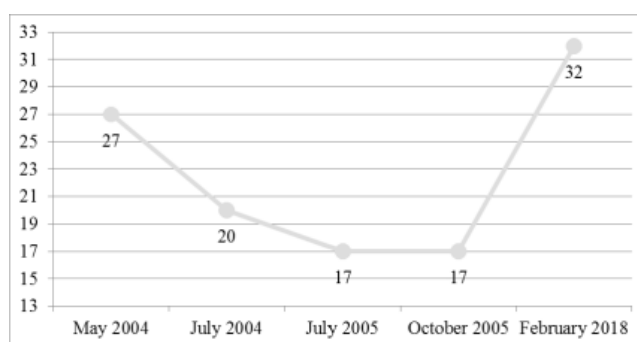

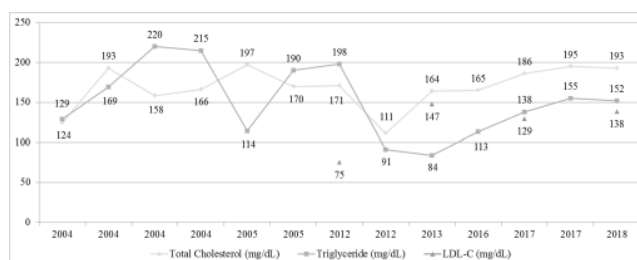**Figure 1.** SLE Disease Activity Index (SLEDAI-2K) between 2004-2018.

Figure 2. Lipid profile between 2004-2018.

Serum complement proteins C3 and C4 were in normal range. Elevated serum C - reactive protein levels (1.4 mg/dL, normal values <0.33 mg/dL) with normal erythrocyte sedimentation rate were found. Severe CKD was confirmed (eGFR: 17 mL/min/1.73m^2), with a normal 24-hour urine protein. Lipid profile, assayed using automated systems (Cobas, Roche Diagnostics) was not remarkable: normal values of total cholesterol and very low-density lipoprotein (VLDL) cholesterol, borderline triglycerides (190 mg/dL). Hyperhomocysteinemia (21.95 µmol/L, normal values <10 µmol/L) and elevated OxLDL (94.6 U/L, normal range: 63.23 +/- 16.23 U/L) were listed.

Laboratory test results throughout disease progression are depicted in Table 1:

Parameters/ Date		May 2004	July 2004	Oct 2004	March 2005	July 2005	Oct 2011	May 2012	Sept 2012	Jan 2013	Aug 2016	Nov 2017	Feb 2018
	ANA 1/40 U/mL	1/1280 (h)	1/640 (h)	1/640 (h)	1/320 (h)	1/640	1/320 (h)						1/320 (h)
Disease activity	dsDNA Ab U/mL	N											N
	C3 60-100 mg/dL	50	76	68	NV	67	55.26						66
	C4 16-40 mg/dL	20	35		NV		25.45						27
Inflammatory markers	CRP<0.1 mg/dL	1.5	2	0.4		0.6							1.4
	ESR<15 mm/h	62	40	76		16			13				18
Blood count	Hgb 12-16 g/dL	11.5	11.7			10.4		8.5	10.1	10.7	11.9	12.5	10.6
	Leu 5-9x10^3/mm^3	6000	2800	2500		4100		4800	3378	2837	6500	6162	5612
	Plt 15-30x10^4/mm^3	300000	236000	212000		229000		152000	147000	121000	140000	206000	151000
Renal function	Creat 0.8-1.2 mg/dL	3.8	2.4	2.3		2.3	2.6	2.66	3.67	3.2	2.7	2.93	3.53
	eGFR mL/min/1.73 m^2	17		31		31	27	25	17	19.8	24	21	18.54
	P/24h <0.15	2,9	2.2	4.5	2.5	5.9	NV	0.075					NV
Addis-Hamburger test	UC Negative	N	N	N		N	N						P
	Ery <1000/min	1500	100	10000		1000	2000						2000
	Leu <1000/min	3000	1300	1000		1000	1000						3000
Lipid profile	TC 150-200 mg/dL	124	193	158		197	170	171	111.6	164	165.4	195	173
	HDL-C >55 mg/dL							22	22.6			28.4	36.1
	LDL-C <100 mg/dL								75.2	147		137	138.4
	TG <160 mg/dL	129	169	220		114	190	198	91.2	84	113.6	155	152

Abbreviations: Ab – antibodies; ANA – antinuclear antibodies; C3 – complement component 3; C4 – complement component 4; Creat – creatinine; CRP - C-reactive protein; dsDNA Ab - anti-double stranded DNA antibodies; eGFR – estimated glomerular filtration rate; Ery – erythrocytes; ESR – erythrocyte sedimentation rate; HDL-C – high-density lipoprotein cholesterol; Hgb – haemoglobin; h – homogenous; Leu – leucocytes; LDL-C – low-density lipoprotein cholesterol; N – negative; NV – normal values; P – positive; 24-UP – 24 hour urine protein test; Plt – platelets; TC – total cholesterol; TG – triglycerides; UC – urinary casts.

ECG recording identified AF with moderate ventricular response, LVH, myocardial ischemia patterns in anterolateral leads.

Echocardiographic data (Vivid E9™, General Electric Company, Boston, MA, USA) described hypertrophy (LHV) and dilation of the left ventricle with HFmrEF, moderate mitral and pulmonary regurgitation, and mild pulmonary systolic hypertension (Figures 4, 5, Table 2).

Lower limbs Duplex ultrasound scanning (HD 11XE™, Koninklijke Philips Electronics N.V., Netherland) identified distal occlusion of the left anterior tibial artery; with no significant atherosclerotic plaques in other predictable arterial areas.

Coronary CT angiogram or left ventriculography were not performed (severe CKD).

Unexpected severe CAD (triple vessel disease) was found on coronary angiogram (Allura Xper FD10 X-ray system, Koninklijke Philips Electronics N.V., Netherland): significant left main distal stenosis, sequential stenosis and aneurysms of left anterior descending artery, occlusion of circumflex artery, significant stenosis of marginal branch and vertical segment of right coronary artery, with retrograde filling of left circumflex artery (Figures 6, 7, 8).

Either conservative approach or concomitant medical therapy and myocardial revascularization procedures (CABG vs. incomplete PCI) were considered, despite SYNTAX II score ≥32[10]. An unacceptable surgical risk based on EuroSCORE II and STS scores and concomitant administration of corticosteroids were assumed by a high-volume heart-team. Successive percutaneous coronary interventions procedures were deemed as inappropriate. Finally, a conservative approach (Bisoprolol 5 mg bid, Amlodipine 10 mg od, Furosemide 40 mg bid and potassium supplementati-
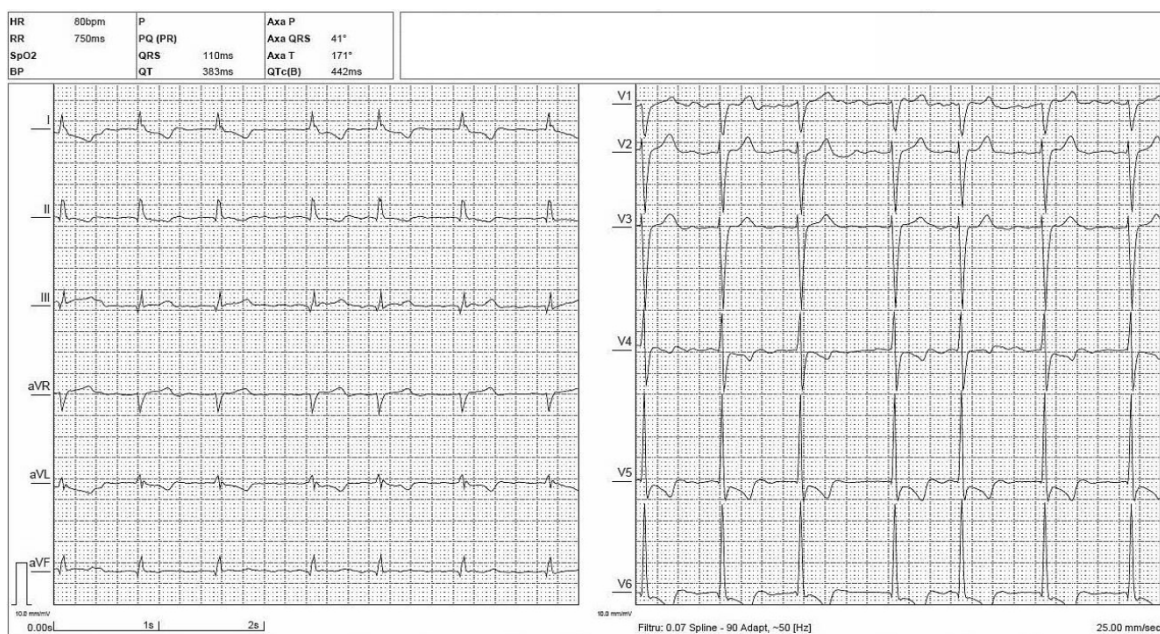

Figure 3. ECG recording at admission.

| Table 2. Transthoracic echocardiographic measurements	
Measurements	**Values**
LV dimensions	IVS: 12 mm, LVPW: 12 mm (concentric hypertrophy)
LV diastolic diameter	68 mm
LVEF (global)	40-49%
Ascending aorta	39 mm
Mitral regurgitation	Grade II
Aortic regurgitation	Grade I
Tricuspid regurgitation	Grade II
Pulmonary regurgitation	Grade II
Pulmonary artery pressure (systolic)	PAPs: 35 mmHg
Abbreviations: LV – left ventricle, IVS – interventricular septum, LVPW – left ventricular posterior wall, LVEF – left ventricular ejection fraction, PAPs – pulmonary arterial pressure (systolic).	
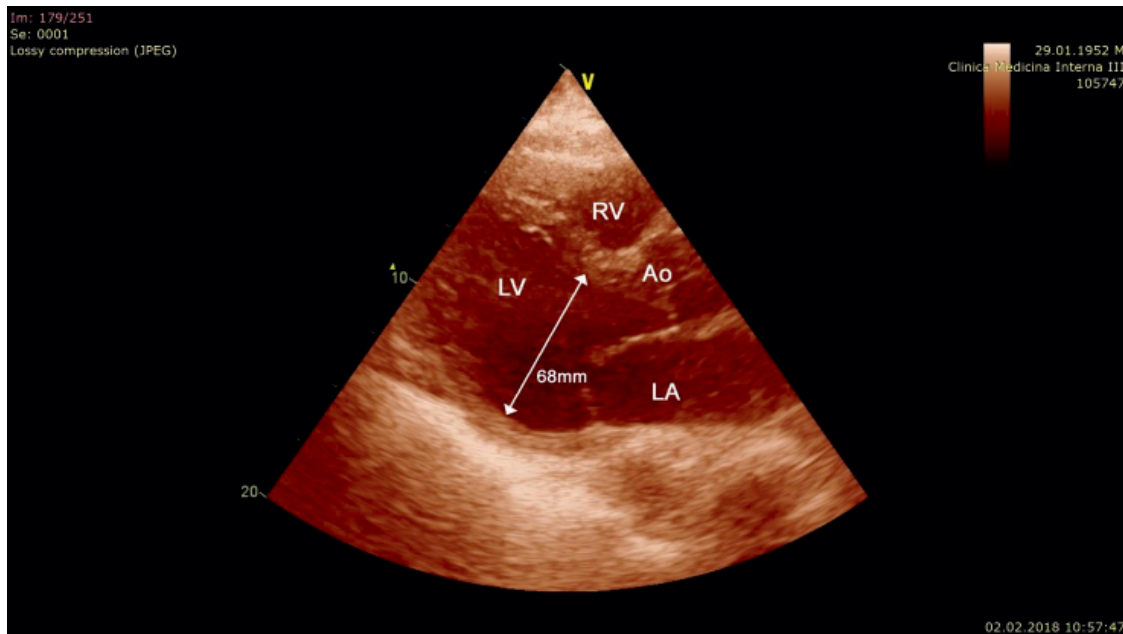
Figure 4. Enlarged left ventricle (parasternal long-axis view).
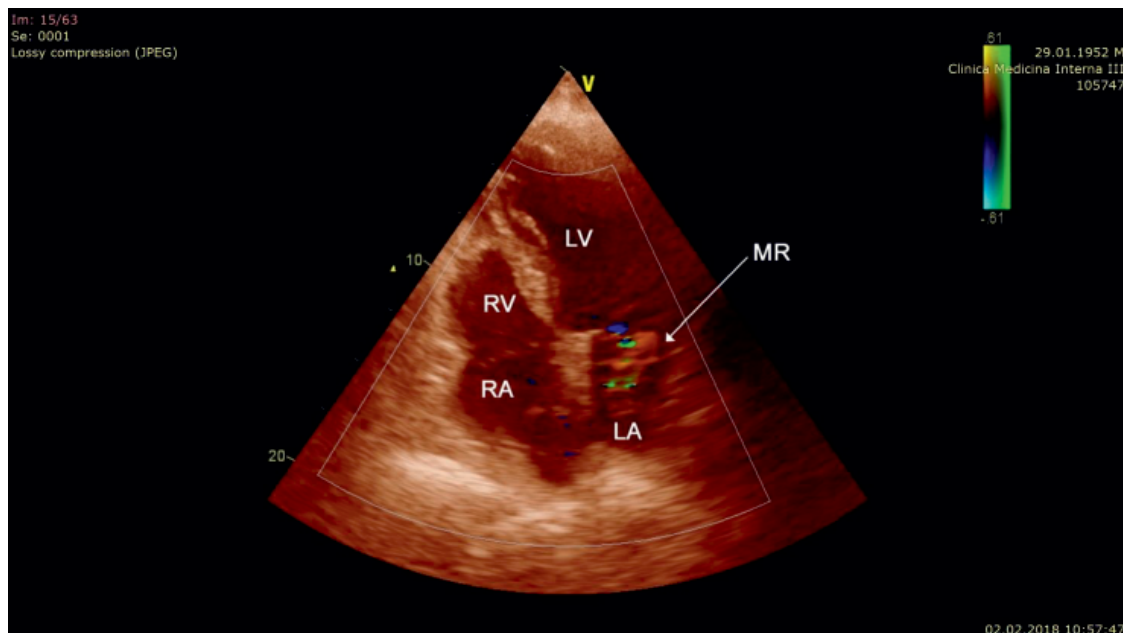Abbreviations: Ao – aorta, LA – left atrium, LV – left ventricle, RV – right ventricle.

Figure 5. Moderate mitral regurgitation (apical 4 chambers view).
Abbreviations: LA – left atrium, LV – left ventricle, RA – right atrium, RV – right ventricle, MR – mitral regurgitation.

on) was offered in patient-centered therapeutic regimen of HFmrEF, secondary hypertension, and CKD.

With no prior medical history of an acute left inferior limb ischemic episode, an embolic etiology of the left anterior tibial artery occlusion was ruled out.

Anticoagulation regimen in the presence of AF EHRA II score, CHA_2DS_2-VASc=4, and HAS-BLED=4 scores had to be decided. NOAC's (Apixaban, Rivaroxaban, Dabigatran) were excluded with respect to concomitant severe CKD and prolonged corticosteroid treatment. Vitamin K antagonist (Acenocoumarol) was proposed as a life-long anticoagulation INR-adjusted regimen.

Non-organ specific SLE therapy consisting of Prednisone 10 mg od along with Atorvastatin 80 mg od was recommended. SLE induced atherosclerosis and documented CAD required statins, benefits of this pharmacotherapy being indisputable[11,12].
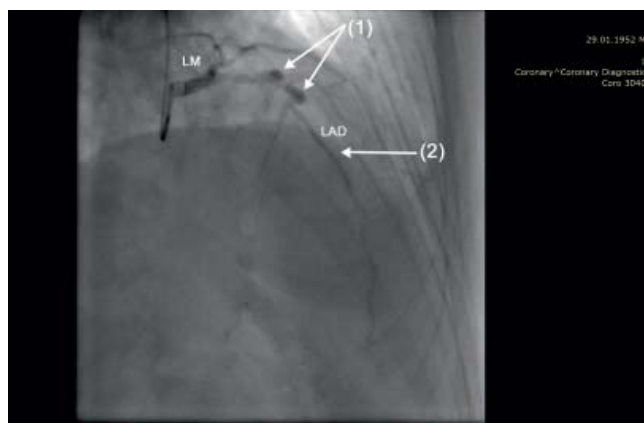
Figure 6. Left coronary angiogram: LM – left main coronary artery, LAD – left anterior descending artery. Arrows indicate LAD aneurysms (1) and severe stenosis (2).
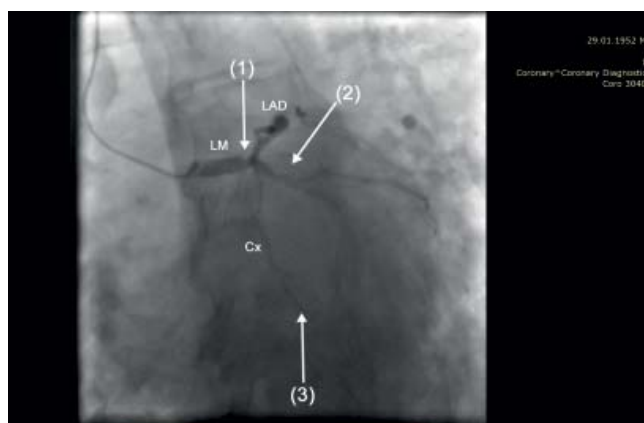

Figure 7. Left coronary angiogram: LM – left main coronary artery, LAD – left anterior descending artery, Cx – circumflex artery. Arrows indicate LM (1) and marginal branch (2) stenosis, respectively Cx occlusion (3).
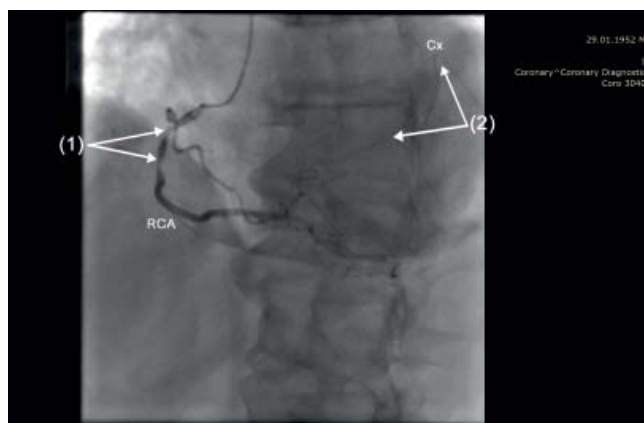

Figure 8. Right coronary angiogram: RCA – right coronary artery, Cx – circumflex artery. Arrows indicate RCA stenosis (1) and collaterals to occluded Cx (2).

DISCUSSIONS

In the SLE population, traditional risk factors for CVD are reinforced by cardiovascular risk factors secondary to SLE, such as the presence of pro-inflammatory cytokines, inflammatory mediators, antiphospholipid antibodies (APL), and antibodies against HDL cholesterol[13].

At the time of diagnosis, 36.3% adult SLE patients experienced dyslipidemia, while 60% develop altered lipidic profiles after 3 years assessment[14,15]. Specific SLE dyslipidemic profiles can either be related to active disease[16] or secondary to corticotherapy[17,18]. Nevertheless, a clear distinction between the two profiles cannot be established.

Lupus patients, particularly those with active disease, present a specific dyslipidemic profile with low HDL cholesterol, high triglycerides, increased VLDL cholesterol, and normal to high LDL cholesterol[19]. Abnormal serum homocysteine[20] and an important proinflammatory state also contribute to atherosclerotic disease in SLE patients as early atherosclerosis is acknowledged as the primary cause of mortality[2].

In healthy individuals, hyperlipidemia is lowered by means of HDL and other newly discovered adaptive mechanisms such as an endogenous molecule, Del-1 (Developmental Endothelial Locus-1) that can bind to oxLDL and inhibit binding to oxLDL receptors[21]. These mechanisms are not sufficient in SLE patients due to the presence of persistent dyslipidemia, renal disease, oxidative stress that leads increased production of OxLDL, and occurrence of antibodies against the protein contents of HDL that cancel the protective effects of HDL[22].

Increased disease activity in SLE patients has been recognized as a potential non-traditional atherosclerotic risk factor, as the incidence of cardiovascular events was reported to be elevated in these individuals[23]. However, due to important discrepancies between the studies design and the activity indices used, inconclusive results have been reported and an increased disease activity in SLE has not been validated yet as a potential cardiovascular risk factor[24].

Our patient presented a constant active SLE with an increased SLEDAI score after a long-term disease progression due to considerable organ damage and suboptimal immunosuppressive treatment. Accordingly data from previous studies[25], his lipid profile was modified, most likely as a result of increased disease activity but also long-term corticotherapy and CKD; however, lipid values were not as excessive in order

to justify the significant CAD. Important CAD burden requires secondary intensive statin treatment, atorvastatin 80mg daily[12]. In the SATURN trial, high statin doses proved to have a significant effect on plaque regression in patients with CAD. Due to his important plaque burden with increased risk of coronary plaque rupture, we considered that the patient would benefit most from the recommended doses of atorvastatin[26].

Glucocorticoid treatment has been long known to correlate with CVD and atherosclerosis in the SLE population[27]. A 10 mg/day or more of corticosteroids correlates with an incremental risk of CV events. Long-term use of 5 mg daily of Prednisone or less is associated with an acceptable low level of CV damage, while the use of more than 10 mg daily of Prednisone is associated with an increased level of CV impairment[28].

Hyperhomocysteinemia (HH) represents an independent risk factor for atherosclerosis leading to premature CVD[29], as it can enhance atherosclerosis by increasing oxidative stress and maintaining a pro-inflammatory state[30]. Common causes of HH are age, vitamin deficiency, impaired renal function with reduced glomerular filtration rate and mutations in genes responsible for the homocysteine metabolism. HH has been shown to correlate with premature atherosclerosis[31], coronary artery calcification[32,33] progression of atherosclerosis[34,20], disease severity and thrombotic risk[35], in SLE patients, with and without renal function impairment. Detected mild homocysteine increase undoubtedly contributed to advanced CAD. Even, though HH lowering therapy is available (folic acid and B-vitamins), the outcome on atherosclerosis progression is discouraging. However, in placebo-controlled clinical trials, mild HH level are lowered, unimpressive results have been reported, as HH lowering therapy failed to have a significant impact on atherosclerotic CVD and/or athero-thrombotic CAD[36].

Kidney disease is recognized as a consistent atherosclerotic risk factor in SLE patients, particularly in cases with poor control. Increased oxidative stress induced by LN and advanced CKD is attributable. In the general population, lower eGFR is associated with a higher CVD risk-related death[37]. In SLE population, in the first 5 years after diagnosis, approximately 60% will develop kidney disease[38].

Kidney involvement was present in our patient at SLE diagnosis; however, the nature of the kidney disease could not be determined due to the lack of a kidney biopsy. Nevertheless, with longstanding kidney

disease he developed renal osteodystrophy and secondary hyperparathyroidism. Elevated serum phosphate is known to be associated with increased arterial stiffness and coronary atherosclerotic plaque calcification in patients with normal kidney function[39]. Higher phosphate serum levels may lead to the formation of calcified atherosclerotic plaques by generating an osteoblastic phenotype in arterial smooth muscle cells[40] and by contributing to the development of endothelial dysfunction[41].

Noticeable in SLE patients an unremarkable dyslipidemic profile can hide an extreme generalized atherosclerotic disease. This specifically applies in situations in which the autoimmune disease cannot be properly controlled due to individual factors, thus leading toward to a persistent inflammatory state; advanced CKD which further enhances inflammation and can lead to hyperphosphatemia and HH (even if treated), will not reduce the atherosclerotic risk directly linked to it[42].

CONCLUSIONS
Long-standing SLE has been recognized as a significant cause of heart diseases. The severity of CAD in the absence of traditional atherosclerotic risk factors reinforces the importance of clarifying the mechanisms underlying the cardiac manifestations of SLE. A close follow-up and patient-centered treatment of SLE patients is mandatory in preventing distinct patterns of cardiac impairment.

Patient provided written informed consent for this paper and additional data of the case.

Conflict of Interest: none declared.

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