Medical Research Archives

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OPEN ACCESS

Published: August 31, 2022

Citation: Da Silva GGTMM, Aragão ACAG., et al, 2022. Sudden Death in a Young Male Patient: When Lupus and Cardiovascular Disease Intersect, Medical Research Archives, [online] 10(8). https://doi.org/10.18103/mra.v10i8.2979

DOI
https://doi.org/10.18103/mra.v10i8.2979

ISSN: 2375-1924

CASE REPORT

Sudden Death in a Young Male Patient: When Lupus and Cardiovascular Disease Intersect

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ABSTRACT

Herein we present the case of a 27-year-old male patient who was recently diagnosed with Systemic Lupus Erythematosus (SLE) associated with nephritis with atypical findings on kidney biopsy and premature cardiovascular disease despite scarce traditional risk factors and negative laboratory findings for antiphospholipid syndrome. A literature review on the epidemiology and pathogenesis of coronary disease in SLE was conducted. The patient was admitted for pulse therapy after refractory disease on outpatient care but evolved with ventricular fibrillation secondary to acute thrombosis in the proximal segment of the anterior left descending artery, with no evidence of atherosclerotic disease. Laboratory findings were also negative for antiphospholipid syndrome both upon diagnosis and after the coronary event. He underwent manual thrombus aspiration and angioplasty with a drug-eluting stent, successfully weaning off mechanical ventilation and vasopressors at the intensive care unit and showing no neurological deficits or left ventricular function impairment. Kidney biopsy later resulted positive for immunoglobulin A nephropathy. The patient was discharged asymptomatic on guideline-directed therapy for coronary disease, warfarin associated with clopidogrel, anti-hypertensive drugs and a combination of immunosuppressants, remaining well on three-month follow-up. SLE is a chronic inflammatory disease that has increasingly been recognized as a major cardiovascular risk factor due to a variety of mechanisms involving accelerated atherosclerosis and thrombosis. As patients survive the first years of disease onset from infection and disease-specific complications, cardiovascular outcomes become a great concern. However, early events such as in this case are possible, especially in the context of flaring disease. We emphasize the importance of an interdisciplinary approach to such patients for better outcomes.

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that causes a constellation of clinical manifestations throughout a patient's lifespan, which makes its diagnosis and treatment challenging, ultimately leading to impaired multiorgan function. The way treatment has evolved in the last decades on one hand promoted improved life expectancy by overcoming infection and disease-specific complications, such as renal failure; on the other hand, it allowed for a greater incidence of cardiovascular outcomes according to different cohort studies.[1,2]

Even though pericarditis is the hallmark manifestation of SLE in the heart, much has been investigated on the participation of specific autoantibodies on endothelial dysfunction, lipid metabolism and plaque disruption. Interferon-δ, interleukin-6 and tumor necrosis factor all play a role in SLE-driven inflammation, contributing to plaque development, foam cell formation and lipoprotein levels imbalance.[3–6] Neutrophils and neutrophil extracellular traps lead to increased oxidation, citrullination and production of cytokines that result in coagulation, thrombosis and endothelial damage.[7–9] High-density lipoproteins become unable to promote cholesterol efflux from the plaque, acquiring pro-inflammatory properties (piHDL).[10] Cross-reactivity of oxidized low-density lipoproteins with autoantibodies also seems to be related to thrombosis and atherosclerosis.[11,12] Such mechanisms translate into accelerated atherosclerosis and a thrombogenic state, leading to a wide spectrum of cardiovascular manifestations, from sudden cardiac death and stroke to stable coronary disease.[2,13,14]

Patients with SLE have a two to three-fold greater risk of having an acute myocardial infarction (AMI) as compared to the general population, according to Yazdany et al.[2] Systemic Lupus International Collaborating Clinics (SLICC) damage index (SDI) is an independent predictor of carotid plaque and correlates with a higher incidence of cardiovascular disease (CVD). The presence of proteinuria and a decreased creatinine clearance are established risk factors. Antiphospholipid antibodies are, in turn, independent risk factors for AMI, stroke and cardiac death.[15–20] The chronic use of glucocorticoid is also associated with an increased prevalence of traditional cardiovascular risk factors and as consequence atherosclerosis.[15,16,21] As a result, stratification tools such as Framingham Risk Score underestimates cardiovascular risk in this population.[22,23]

Case report

A previously healthy 27-year-old male patient noticed in October, 2021, the appearance of erythematous nodular skin lesions on the scalp, predominantly in the occipital region, that later on spread out to the thorax and upper limbs. The patient sought medical assistance from a dermatologist. Skin biopsy demonstrated an interface dermatitis with moderate perivascular lymphocytic infiltrate, associated with thickening of the basement membrane and the presence of interstitial mucin, which were indicative of cutaneous lupus. Laboratory assays turned positive for antinuclear factor (ANA, with a homogeneous nuclear pattern at 1:320), anti-Ro and anti-Smith antibodies. A trial on topical clobetasol was initiated with modest results. Five months from onset the patient developed malar rash, non-scarring alopecia, myalgia, fever and arthralgia involving the hands, wrists and ankles with morning stiffness. In March, 2022, the assisting rheumatologist, upon establishing the diagnosis of SLE, started a combination of hydroxychloroquine (400 mg once a day), azathioprine (50mg twice a day) and prednisone (5 mg once a day). After three weeks of drug therapy, the patient's condition improved despite persistent cutaneous lesions. New complementary exams showed an increased ANA (a homogeneous nuclear pattern at 1:640), positive anti-double-stranded DNA, positive antinuclear ribonucleoprotein antibody, negative antiphospholipid antibodies (aPL) and decreased levels of both C3 and C4 complement. Urinalysis demonstrated microscopic hematuria (5 – 8 red blood cells per high-power field) and mild proteinuria (1 plus), while 24-hour urine sample showed 375mg of proteinuria. Chest computed tomography scans and transthoracic echocardiogram were clear. Due to the presence of active urinary sediment associated with positive anti-double-stranded

DNA antibody and reduced complement, the possibility of rapidly evolving nephritis was a concern. In April 2022, the patient was admitted to the hospital in good general condition for elective renal biopsy and induction therapy with methylprednisolone 1g once a day for three days combined with mycophenolate mofetil 500mg twice a day. The procedures were uneventful and upon discharge on the fourth day of hospital stay the patient experienced excruciating oppressive chest pain. Electrocardiogram indicated anterior wall ST segment elevation AMI (figure 1), prompting immediate coronary angiography. While trying to puncture right radial artery, ventricular fibrillation (VF) ensued. After 15 minutes of cardiopulmonary resuscitation (CPR) associated with intense electrical instability the return of sinus rhythm and spontaneous circulation was achieved. A femoral artery access was obtained, and a large thrombus was identified (figure 2) in the proximal segment of the Left Anterior Descending Artery (LAD) with no evidence of atherosclerotic disease. The patient underwent thrombus aspiration (figure 3) and angioplasty with a drug-eluting stent through a right femoral vascular access. Intracoronary tirofiban was used because of the high burden of thrombus and distal embolization. He was admitted to the cardiac intensive care unit sedated on mechanical ventilation and stable on norepinephrine. The patient presented a favorable course with no neurological deficit, weaning off mechanical ventilation within 24 hours. Transthoracic echocardiogram indicated a preserved left ventricular ejection fraction and apical segmental dysfunction. Cardiac magnetic resonance (figure 4), obtained two weeks after the event, showed absence of myocardial viability restricted to the distal third of the LAD resulting in 3% of infarcted mass. No other cause for coronary thrombosis was identified on transesophageal echocardiogram and 24-hour Holter monitoring. In addition to guideline-directed therapy after AMI, prednisone was maintained on 0,5mg/kg/day and mycophenolate was titrated to 1000mg twice a day. Hypertension was controlled by a combination of three drug classes. Although initially on triple antithrombotic therapy (aspirin, clopidogrel and full-dose enoxaparin), the patient was discharged on warfarin and clopidogrel alone, given the possibility of APS in spite of negative specific autoantibodies. Subsequently, renal biopsy showed granular mesangial deposits of immunoglobulin A (IgA) with a diffuse pattern and of C3 complement factor with focal distribution, ruling out the diagnosis of lupus nephritis (LN) and suggesting an IgA nephropathy (IgAN) associated with SLE.

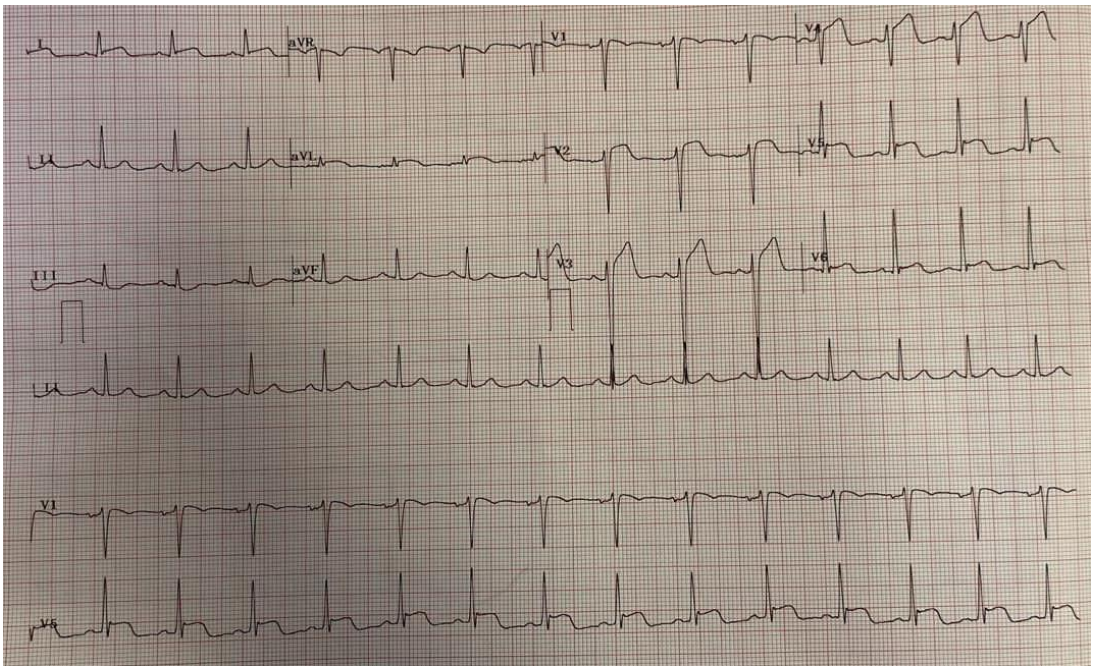

Figure 1 - Initial electrocardiogram showing sinus rhythm with ST-segment elevation in leads I, aVL and V1-6.

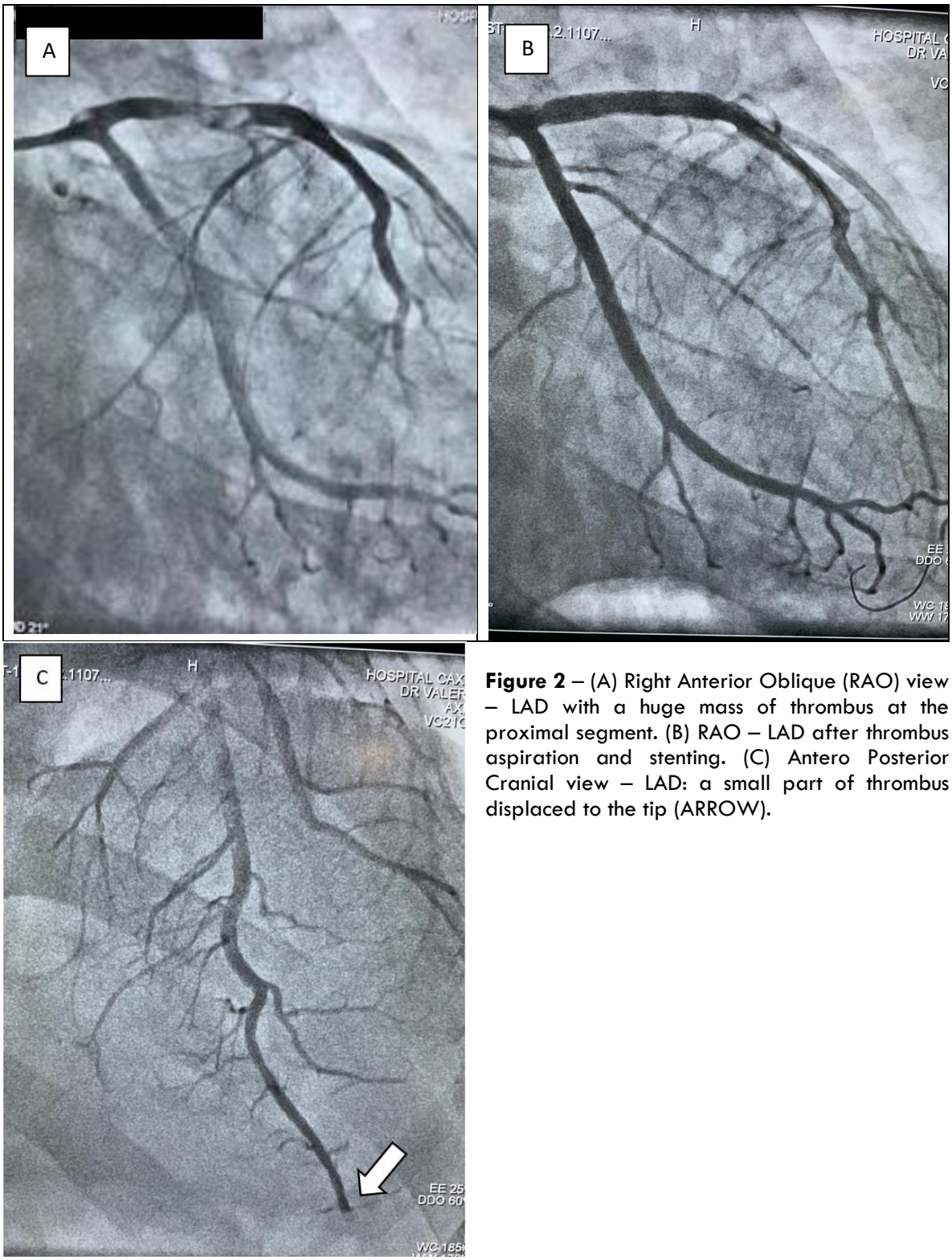

Figure 2 – (A) Right Anterior Oblique (RAO) view – LAD with a huge mass of thrombus at the proximal segment. (B) RAO – LAD after thrombus aspiration and stenting. (C) Antero Posterior Cranial view – LAD: a small part of thrombus displaced to the tip (ARROW).

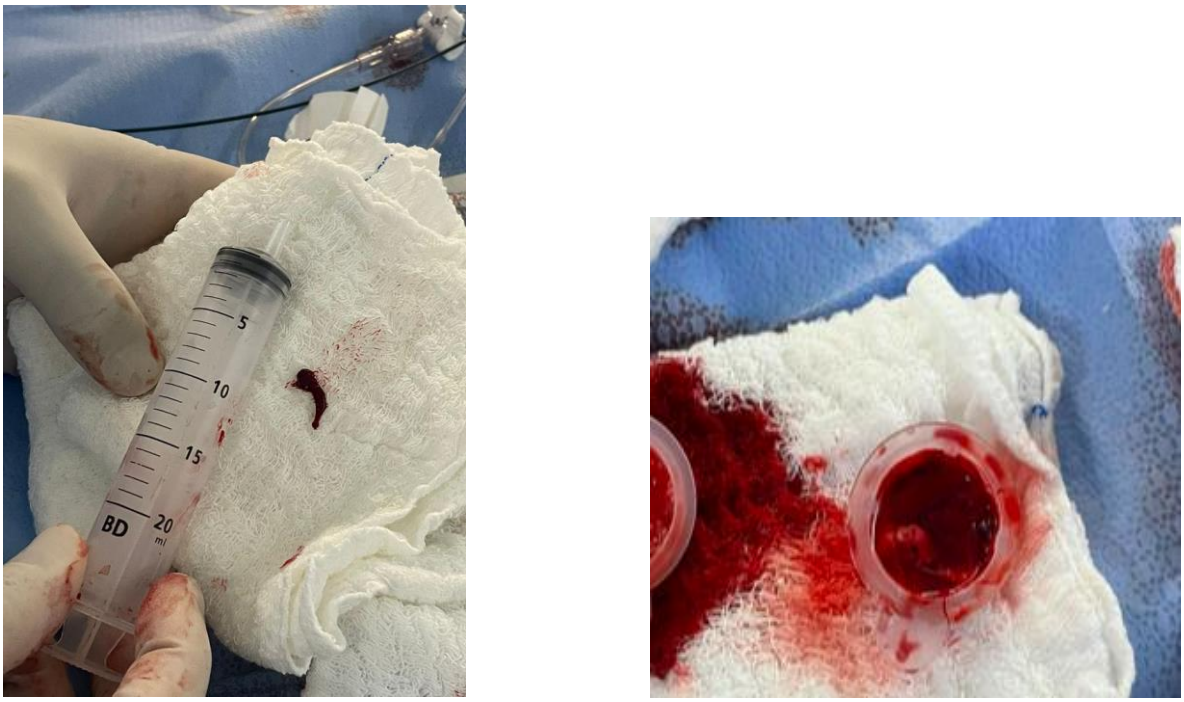

Figure 3 - A large red thrombus and thrombotic material was aspirated.

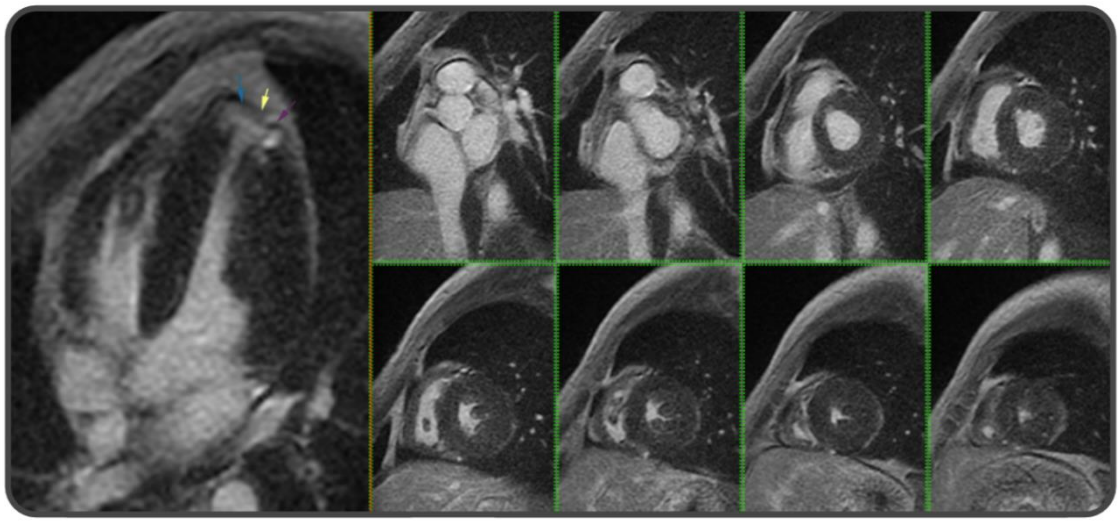

Figure 4 - Cardiac magnetic resonance showed absence of myocardial viability restricted to the distal third of the LAD, resulting in 3% of infarcted mass.

Discussion

The present case report depicts a previously healthy young male patient who had been recently diagnosed with SLE and survived a sudden death due to acute coronary thrombosis in LAD. Due to absence of atherosclerotic burden in the angiographic study, secondary APS was suspected as the main etiology of the coronary event despite negative aPL.

Cardiac involvement in SLE usually presents as pericarditis. Although, valvular heart disease and, more rarely, myocarditis can be detected.[14] The most characteristic valve disease of SLE is Libman-Sacks endocarditis, which primarily affects the left heart valve.

Furthermore, coronary heart disease is frequent among these patients and the most common causes of myocardial infarction in this context include atherosclerosis, thrombosis, embolization, or vasculitis. [14,24]

The skin lesions in our patient were the first sign of disease and correlate with vasculitis, which can occur in approximately 50% of SLE patients.[25] Lupus vasculitis (LV) usually involves small vessels, although medium-sized vessels can be affected, and large vessels involvement is rare. The clinical form depends on the size of the vessels and the sites involved. LV normally appears during active disease and can be associated with APS.[26,27] The skin is affected in 90% of the cases. Less frequent is the involvement of the nervous system gastrointestinal tract, lungs, kidney, and heart. Few cases of valve dysfunction and myocardial dysfunction due to small vessel vasculitis have been reported.[25,28] Coronary vasculitis is rare in SLE and angiography findings includes isolated segments with tapered narrowing, the presence of coronary ectasia, or aneurysms. [24,29]

Mortality in SLE is either associated with CVD, infection or disease activity, mainly LN and central nervous system lupus. [30,31] In Brazil, the main causes of death are infection and renal failure, while in developed countries cardiovascular causes figure among the most prevalent. [32] Cardiovascular death occurs in average nine years from disease onset, especially in the sixth decade of life and mostly in women, while death from infection and disease activity occurs in the early years of diagnosis. [30,33]

Research has associated premature cardiovascular death with accelerated atherosclerosis. [34] In contrast, in patients with primary APS the etiology is due to thrombosis in previously normal coronary arteries, mostly in young patients. When SLE is associated with APS, the occurrence of AMI may differ from that commonly seen in APS, premature atherosclerosis is estimated to be at least 2-fold higher. [34–36] In the Euro-phospholipid cohort study, among 1,000 APS patients, the group with combined SLE had a significantly higher risk of AMI (3.8% vs. 1.2 %; $p < 0.05$). [37]

The pathophysiology of accelerated atherosclerosis in lupus is not fully understood. It appears to be multifactorial, involving vascular damage with endothelial dysfunction, dysregulation of innate and adaptive immune response, and other causes such as dyslipidemia, hyperleptinemia, chronic glucocorticoid use, azathioprine, and insulin resistance. These factors, therefore, favor endothelial damage, vasculopathy, and a proatherogenic and thrombotic state that result in CVD. [14,38]

Endothelial cell (EC) dysfunction is one of the first signs of CVD. In SLE, atherosclerosis is associated with a decrease in the number of circulating endothelial progenitor cells and dysfunction of cells involved in vascular repair, such as reduced production of endothelial growth factor and hepatic growth factor. In addition, some cytokines and adhesion molecules, such as tumor necrosis factor alpha, interleukin-1 alpha, vascular cell adhesion molecule, intercellular adhesion molecule and E-selectin are upregulated in SLE and associated with higher coronary calcium scores. [34,39–41]

According to Nhek et al., SLE can lead to platelet activation, which consequently stimulates EC and pro-inflammatory mediators, triggering an imbalance between EC damage and repair. [42] Therefore, it can be inferred, according to the study by Taraborelli et al., that endothelial dysfunction and arterial stiffness are common in people with lupus who do not have known risk factors for CVD.[43]

Clinical predictors of cardiovascular events (CVE) associated with SLE can be divided into two groups: traditional risk factors and SLE-related factors. In the first group, the main factors are male gender, family history of coronary heart disease, dyslipidemia, hypertension, diabetes, and smoking. In the second group, the greatest correlation of risk is the presence of aPL, followed by drug therapy with corticosteroids and immunosuppressants, especially azathioprine. In addition, evidence has shown that renal and neuropsychiatric disorders also increase the risk of CVE.[2,44–46]

Apart from being male, our patient did not have the traditional risk factors for CVE. The patient was a non-smoker and had no family history of coronary heart disease or autoimmune disease. As for disease-related risks, there was no positive aPL either upon diagnostic workup nor after AMI, however he recently used azathioprine and corticosteroids.

The presence of positive aPL, such as anticardiolipin antibodies, lupus anticoagulant

(LA) and anti-β2-glycoprotein-I antibodies, occurs in 30-40% with SLE.[47] Approximately 40% of SLE patients with positive aPL develop venous and/or arterial thrombosis, compared with 10-20% of negative aPL.[48] In addition, vitamin K and heparin antagonists interfere with LA tests and may mask positive results. On the contrary, direct oral anticoagulants (DOACs) can prolong LA clotting time. Therefore, guidelines recommend that LA tests not be performed while on warfarin with an INR greater than 1.5 and only performed 2 to 3 days after the last dose of DOACs.[49,50]

Glucocorticoids tends to increase the lipid profile, blood glucose, body mass index and systolic blood pressure. Therefore, its prolonged use becomes an independent risk factor for CVE.[51] However, because of the short course of glucocorticoids, it cannot be considered as a relevant risk factor in this case, although it must have played some role as an adjunct to the thrombotic event.

Approximately 50% of patients with SLE have renal involvement, largely due to LN.[52] LN is an independent predictor of CVE.[45] It usually presents a "full house" pattern, characterized by immunofluorescence microscopy staining of C3, C1q complement, immunoglobulin G, A and M. However, in the present case biopsy showed dominant deposits of IgA, characterizing IgAN. SLE associated with IgAN is rarely described in the literature, even though it is the most prevalent primary nephropathy worldwide.[52,53]

Conclusion

The present case of premature sudden cardiac death in a young male patient with recently diagnosis SLE is intriguing. It is unlikely that a previously healthy patient with absent traditional risk factors for CVD, low SLICC damage index (two points) and a short course of glucocorticoids and immunosuppressants would present such a catastrophic coronary event. The diagnosis of secondary APS is challenging in this scenario since negative laboratory results before a thrombotic event or under anticoagulation cannot rule out the disease. Therefore, the assisting medical team insisted on long-term anticoagulation therapy with warfarin. In conclusion, SLE sets patients at high risk of adverse cardiovascular outcomes that can be underestimated by current risk stratification tools. An interdisciplinary approach is key to provide adequate and timely medical assistance to such patients, given the complexity of this multisystemic disease.

Conflicts of Interest Statement

No potential conflict of interest relevant to this article was reported.

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