Heart disease characteristics in patients with systemic lupus erythematosus

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SUMMARY

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by periods of activity and remission in which any organ can be affected. Cardiovascular involvement represents an important cause of mortality in SLE patients after infections. Indeed, valvular involvement in a patient with cutaneous lupus is considered the first sign of a systemic condition. These patients may have an isolated condition in the pericardium, myocardium, endocardium, valves and vascular bed or an overall involvement. Cardiac alterations may be present in more than 50% of patients at any stage of disease progression, especially in men, who have a higher risk of cardiovascular disorders. This paper is a review of the characteristics of cardiac involvement in SLE patients and its clinical manifestations, diagnosis and treatment.

KEY WORDS

Atherosclerosis; Cardiovascular diseases; Systemic Lupus Erythematosus; Morbidity; Mortality

RESUMEN

Características de la afección cardíaca de los pacientes con lupus eritematoso sistémico

El lupus eritematoso sistémico (LES) es una enfermedad de etiología autoinmune caracterizada por episodios de crisis y remisiones, en la que se puede afectar cualquier órgano. Luego de las infecciones, las afecciones del sistema cardiovascular explican una parte importante de la mortalidad en pacientes con LES. De hecho, el compromiso valvular en un paciente con lupus cutáneo fue el primer indicio para considerar que esta era una enfermedad sistémica. En dichos pacientes se puede afectar aisladamente cualquier estructura cardiovascular:

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pericardio, miocardio, endocardio, válvulas y lechos vasculares, y también puede ocurrir compromiso global. Las alteraciones cardíacas se pueden encontrar en cualquier etapa de la evolución de la enfermedad y suelen estar presentes en la mitad o más de los pacientes especialmente en hombres, que tienen más riesgo de compromiso cardiovascular. El presente artículo es una revisión de las características de la afección cardíaca en los pacientes con LES; se incluyen sus manifestaciones clínicas, el diagnóstico y el tratamiento.

PALABRAS CLAVE

Aterosclerosis; Enfermedades Cardiovasculares; Lupus Eritematoso Sistémico; Morbilidad; Mortalidad

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by periods of activity and remission. Cardiac conditions are common in SLE and were one of the first symptoms described in the literature. All cardiac structures, the pericardium, myocardium, endocardium, valves and vascular beds, may be affected individually or as part of an overall condition (1,2) that varies in its frequency and severity (3). The correct diagnosis and treatment are based on the clinician's understanding of the frequency, etiology and clinical presentation of cardiac involvement in SLE patients. In this article, the characteristics, clinical manifestations, diagnosis and treatment of these conditions are reviewed.

PERICARDIUM INVOLVEMENT

Pericarditis is one of the most common findings in SLE patients, and it is included among the American Rheumatism Association/American College of Rheumatology (ARA/ACR) classificatory criteria. This condition is reported in 25% to 50% of patients, depending on the series (4,5), and is mostly asymptomatic. Cardiac tamponade may be the initial manifestation of the disease; it is present in 1% to 4% of cases (6-8). Pericarditis may be acute or chronic (9) or may have other presentations, such as hemopericardium (10,11).

Immunofluorescence studies show immunoglobulin and C3 complement deposits, which suggest that pericarditis is mediated by immune complexes, although this hypothesis is not completely clarified (12). Moreover, pericardial effusion is produced by a decrease in the lymphatic and venous flow of the myocardium secondary to increased pressure in the right atrium and hypoalbuminemia.

Pericarditis occurs most frequently in women. Together with other organ involvement, it may present dull precordial pain (39%), dyspnea (61%) and pericardial friction rub (6%) (2,13). Typical electrocardiographic changes (39%), cardiomegaly on chest radiographs (44%) and pericardial effusion on echocardiogram (94%) are often seen in paraclinical studies (14). Patients with pericarditis have lower levels of albumin, serum proteins and C4, as well as proteinuria, high C-reactive protein (CRP) and a positive score for SLE disease activity (4,15).

Mild involvement can be treated with NSAIDs or low doses of steroids, and severe involvement can be treated with intravenous methylprednisolone. Other immunosuppressants have been used in recurrent cases (13). Cardiac tamponade cases and those that do not respond to drug therapy may require surgery (16).

MYOCARDIAL DISEASES

Based on autopsy studies, 40% to 60% of SLE patients have myocardial involvement, but only 5% to 10% show clinical manifestations. In a retrospective study, Law *et al.* (17) identified, over an eight-year period, 11 cases of myocarditis as systolic function involvement on an echocardiograph with no evidence of coronary disease. This result sustains the rareness of clinical lupus myocarditis. All of the patients were females, and for eight of them, myocardial involvement was the initial manifestation of lupus (73%).

Histopathological examination of SLE cardiomyopathy shows mononuclear perivascular and interstitial invasion with myocardial degeneration and fibrosis (18,19) as well as immune complexes and complement deposits on the vascular walls and in the perivascular spaces (12). For unknown reasons, these findings appear on the posterolateral segments and are similar to those of viral myocarditis (20). Findings similar to giant cell myocarditis have been reported in the literature (21).

The clinical features of dyspnea (76%), edema, orthopnea and crepitus (72%), tachycardia and jugular venous distension (54%) or cardiogenic shock are indistinguishable from other types of myocarditis (22). In more than half of the patients, other systems are involved, particularly the skin, kidneys, central nervous system and gastrointestinal tract (17). Laboratory findings show lymphopenia, complement consumption, positive anti-DNAs, lupus anticoagulant (LA) and elevated creatine kinase. Additionally, some reports associate lupus myocarditis with elevated anti Ro/SSA (23). Diffuse contractility involvement with or without a decrease in ejection fraction in echocardiography (24), disorders on the myocardial perfusion scintigraphy (25,26) and, recently, abnormalities on magnetic resonance imaging (27-29) sustain the diagnosis.

Regardless of the severity of the condition, prompt treatment with high doses of steroids is required. Cyclophosphamide (22,30,31) and intravenous immunoglobulin (IVIG) (32) have also been used to treat lupus myocarditis.

Because myocardial involvement can be linked to atherosclerosis, high blood pressure, nephropathy, heart valve disease or toxic reaction to drugs, its association with lupus is hard to define and must be considered a diagnosis by exclusion (13).

VALVE INVOLVEMENT

Valve involvement is common in SLE patients, particularly in those with positive lupus anticoagulant. The prevalence of this condition is variable and will depend on the study: 13% to 65% on autopsies, 9% to 28% on transthoracic echocardiograms (TTE) (33,34) and 53% to 73% on transesophageal echocardiogram (TEE) (35).

Although its physiopathology is not clear, it is thought to have an immunological basis because of the association with lupus anticoagulant, immune complexes deposits in the valves, especially in interaction with anticardiolipins and anti-β2-glycoprotein-I, and the positive response to steroids (1). The most common finding is the thickening of the left heart valves, followed by Libman-Sacks endocarditis and other non-specific lesions. Valve regurgitation prevails, while stenosis is rare (36).

A study that analyzed the echocardiograms and myocardial perfusion of 60 asymptomatic patients identified an association between valve involvement and disease progression (more than eight years), elevated CRP levels and reduced C3 and C4 levels. An association was found between perfusion defects and an increase in the right ventricle pressure, with higher levels of anticardiolipin IgG and anti-β2-glycoprotein-I (37). Furthermore, Jensen-Urstad *et al.* identified an association between valve involvement and elevated VLDL, triglycerides and homocysteine (38).

Patients with valve involvement may have serious complications, such as cerebrovascular events, peripheral embolism, infectious endocarditis and heart failure (35); however, there is no specific therapy for these patients other than the standard treatment for SLE.

Libman-Sacks endocarditis

In 1924, Libman and Sacks described postmortem findings of verrucous valvular lesions, especially involving the mitral valve. Histopathological studies have identified two types of lesions: active lesions, characterized by fibrin accumulations, focal necrosis and mononuclear infiltrates, and scarring lesions with vascularized fibrous tissue and calcifications (13).

The vegetations are located on the base of the valve, making most cases asymptomatic and occasionally resulting in heart murmurs. In 3% to 4% of cases, hemodynamic compromise is present; however, only half of these cases require surgical treatment. Some patients may develop infectious endocarditis (7%), cerebrovascular disease and peripheral embolism (13%). The prevalence of these complications has decreased since the introduction of corticosteroid treatment: these drugs are the treatment of choice (prednisolone 1 mg/kg/day) for symptomatic patients, when necessary.

CONDUCTION SYSTEM DISEASE

These disturbances present with other cardiovascular conditions in 16% of patients and as a single condition in 3.2% of patients (39). Sinus tachycardia is the most common heart rhythm alteration in SLE patients. It can be secondary to fever, anemia, pulmonary embolism and other cardiac abnormalities (13). Nearly

25% of the patients have a shortened PR interval (4). Although rare, second-degree atrioventricular block and complete non-congenital heart block have been described (40,41) and are associated with positive levels of RNPU1 antinuclear antibodies (42), antiRo antibodies and disease activity (41). Among the physiopathological mechanisms proposed, vasculitic disorders, mainly affecting the conduction system, and vacuolar myopathy are described (43). Most patients are asymptomatic; however, atrioventricular blocks with presyncope or syncope have been described.

Because this is an infrequently occurring condition, there is no specific treatment described in the literature for SLE patients other than that described for non-lupus patients who have electrocardiographic findings. However, some cases with AV blocks respond to steroids without the need for a permanent pacemaker (43-45).

HEART FAILURE

Systolic or diastolic left ventricular function involvement is noted in 5% to 31% of SLE patients, secondary to coronary disease (46). On the target organ assessment of the LUMINA cohort study, 42% of patients had isolated heart failure, 4.6% had heart failure associated with acute myocardial infarction (AMI) and 14% had heart failure associated with coronary disease (39). Heart failure hospitalization risk is 3.01, 1.39 and 1.33 times more frequent in SLE patients aged 34 to 44 years, 45 to 65 years and older than 65 years, respectively (47).

In a prospective study of 54 patients, diastolic alteration was associated with disease activity (44% versus 3.4%) rated higher than 5 on the SLEDAI index (*Systemic Lupus Erythematosus Disease Activity Index*) (48).Other studies add age and the time course of the disease to this relationship (46). Clinical and paraclinical findings do not differ from those of heart failure with other etiologies.

The treatment of choice for these patients, when needed, is angiotensin-converting enzyme inhibitors (ACE-I), beta-blockers and diuretics.

CORONARY DISEASE AND ACUTE MYOCARDIAL INFARCTION

In 1976, Urowitz's group described a bimodal mortality for SLE patients: an early mortality associated generally with the disease activity, and a late mortality associated with AMI (20% to 45%, depending on the study) (49-52). In recent years, this phenomenon, taken as an inflammatory condition, makes lupus an *in vivo* model of the atherosclerotic process, although an accelerated atherosclerosis in SLE patients is well known.

Clinical cases of atherosclerosis (angina or AMI) account for 6% to 12% of patients or nearly 40% when subclinical cases are included (49,50), although some authors report a prevalence of 95% (39). LUMINA, a very large and multiethnic cohort, established a 6.8% rate of cardiovascular damage in 6.6 years (39).

Lupus increases the risk of having an AMI by 50 times in the 34-to 44-year age range. Lupus carries 8.5 times the risk of hospitalization and 5 times the risk of a cardiovascular event, all at an earlier age than in the general population (51-53).

Although the prevalence of traditional risk factors is high in patients with lupus, it can not explain their elevated frequency in SLE patients (54-56). Three mechanisms for the coronary circulation involvement in SLE patients have been suggested, as follows: arteritis (the rarest), tendency toward thrombosis (57) and accelerated atherosclerosis (58,59).

Traditional risk factors

The International Registry for Atherosclerosis (SLICC-RAS) conducted a multicenter study of SLE patients. At the moment of diagnosis, their average age was 34 years, 33% showed high blood pressure, 36% had dyslipidemia, 16% were smokers and 3.6% had diabetes (60). After three years of follow-up, these percentages had almost duplicated, as 58% had high blood pressure, 60% had dyslipidemia, 43% were smokers and 5% had diabetes mellitus (61). In the Lupus Hopkins cohort study, the percentages were similar: 46% had high blood pressure, 55% had dyslipidemia, 37% were smokers, 6% had diabetes and 70% had a sedentary lifestyle.

The persistence of hypercholesterolemia at the beginning of the disease seems to have an influence on accelerated atherosclerosis (62). Lipid disorders are identified at an early age and have a high prevalence, even in cases of pediatric and juvenile lupus (50% to 85%, depending on the study) (63). Elevated triglycerides and lipoprotein(a) with reduced cHDL and normal or slightly elevated LDL is described as the lupus

dyslipidemia pattern (64). Hayata *et al.*, studying a group of 40 patients with an average age of 20 years, identified that 85% of them had high-risk alterations of lipid disorders, especially reduced cHDL (65).

Metabolic syndrome (MS) is present in 20% to 38% of lupus patients (66-69). MS is more prevalent in SLE patients under 40 years of age (15.8% versus 4.2%) compared with a control population of similar age, while this difference is not seen in older patients. This result suggests that MS inflammatory mechanisms play a predominant role in younger patients and a multifactorial etiology in older patients. These patients have three and eight times higher risks of cardiovascular disease than lupus patients without MS and MS patients without lupus, respectively (68). A late diagnosis, nephrotic-range proteinuria and a high injury rate have been linked to MS (66).

Non-traditional risk factors

Other factors have been related to a higher prevalence of cardiovascular events, such as lipoprotein(a) (70), oxidized LDL and its antibodies, antibodies for HDL and fractional Apo A1 (71), antiphospholipid antibodies, serum amyloid A, low activity of lipoprotein lipase (63), acute phase reactants (CRP, fibrinogen) and hyperhomocysteinemia (49,72).

Serum amyloid A is a protein coexpressed with phospholipase A2 as a factor of accelerated atherosclerosis in SLE patients. When bonded to cHDL, this protein triggers the lipolytic activity of phospholipase A2 that promotes endothelial damage (62).

Lupus anticoagulant is a risk factor for arterial thrombosis, including coronary arteries (73). Among this antibody family, β2-glycoprotein is of great interest because it appears to have atheroprotective effects (74).

Finally, in a 5-year prospective study of 94 lupus patients, early menopause and a slightly higher risk of coronary calcifications seemed to contribute to a higher risk of cardiovascular disease in SLE patients (OR: 1.19; 95% CI: 1.01-1.35) (75).

CARDIOVASCULAR RISK ASSESSMENT IN LUPUS

Despite the large number of indexes used to stratify the risk of the general population, none has achieved a way to correlate a higher incidence of cardiovascular events with lupus. Chung *et al.* compared two index scores for cardiovascular risk (Framingham and PDAY) and the calcium levels of 93 patients with lupus and 63 controls (70). SLE patients had a higher prevalence of coronary calcifications (19.4% versus 6.2%) and a higher calcium score (30 ± 200 versus 4 ± 30 units) but no differences in the risk index scores. Furthermore, 99% of patients had a low risk according to the Framingham index, despite the presence of important coronary calcifications. Other risk scores have been evaluated, such as the Framingham index adjusted to coronary age, the Reynolds Risk Score and the Reynolds Risk Score adjusted to calcium scores, without an adequate stratification of cardiovascular risk (76).

The best method for diagnosing coronary disease in SLE patients is unknown. The correlation between non-invasive studies, echocardiography (77) or gammagraphy and coronarography is low (78).

Korkmaz *et al.* (79) analyzed the cases of AMI reported in the literature for SLE patients under 35 years of age and found 50 cases (41 women and 9 men), with an average age of 20 years. Based on the coronarographic findings, the patients were divided into three groups, as follows: **1.** Normal coronary or thrombosis patients (32%), characterized by an early appearance of the disease, positive lupus anticoagulants and higher activity scores; **2.** Coronary aneurysm or arteritis patients (24%), characterized by a moderate time of evolution of the underlying disease, active disease and high renal involvement; and **3.** Coronary atherosclerosis patients (44%), with longer-standing SLE, a higher frequency of cardiovascular risk factors and an absence of lupus activity.

Therapy depends on the origin of the problem, which can be inflammatory, immune activity-mediated or related to complications of the disease and its treatment or the treatment for another associated process. In general, this treatment is not different from that of the general population (beta-blockers, ACE-I/AIIRA, statins and aspirin). The exception is for vasculitis, which requires 1-1.5 mg/kg/day prednisolone, and the use of anticoagulants and vasodilators for antiphospholipid syndrome (13).

Statins treatment has known effects on lipids and has been shown to reduce levels of anti-DNA and lupus nephritis, for which its use with all SLE patients has

been suggested. However, a recent controlled clinical trial dismisses the clinical utility of this treatment (80). In contrast, a cohort study found a 70% reduction in cardiovascular mortality and an 11-month gain of a healthy life in patients who underwent aspirin treatment. Despite all these data, no clinical study has validated these observations (46).

TREATMENT COMPLICATIONS

Glucocorticoids

Steroids are the backbone of SLE treatment, although they have been linked to cardiovascular risk factors such as dyslipidemia, high blood pressure, carbohydrate intolerance and accelerated atherosclerosis. Moreover, these drugs may increase the adipose tissue in subepicardial areas, especially those around the epicardial arteries, and may also increase the thickness of the right ventricle walls (81). When adjusted for several variables, the Hopkins cohort analysis (49) associated a 10-mg increase in the prednisolone dose with a positive variability of 7.5 ± 1.46 mg/dL total cholesterol, 1.1 mm Hg in mean blood pressure and 5.5 ± 1.23 lb of body weight. In the study, accelerated atherosclerosis was related to the dosage (RR: 1.5; 95% CI: 1.2-2.4) but not to high doses (RR: 1; 95% CI 0.3-3) or methylprednisolone pulses (RR: 1.1; 95% CI 0.7-1.8). Glucocorticoid effects are dual. Low doses protect the endothelium with anti-inflammatory action, but high doses disrupt the cardiovascular metabolism. The line between these two effects varies from one patient to the other. Finally, in the Puerto Rico Cohort (67), 10 mg of prednisolone or of a similar drug increased the risk of metabolic syndrome in SLE patients (OR: 3.69; 95% CI: 1.22-11.11).

Antimalarial drugs

Antimalarial drugs have immunomodulating properties and play an important role in mild and moderate manifestations of lupus. Additionally, antimalarial drugs counteract hypercholesterolemia associated with steroids (a total cholesterol reduction of 8.9 ± 3.44 mg/dL) (49,62). In the Hopkins cohort, hydroxychloroquine showed a protective effect against thrombosis via several mechanisms of lupus activity control, an antiplatelet effect and a reduction in antiphospholipid antibody scores. A negative correlation between antimalarial drugs and high-sensitivity CRP levels has been described. This correlation is a known cardiovascular risk indicator (82). In comparison, Bellomio (69) and Sabio (83) found a reduction in the risk of metabolic syndrome after the use of antimalarial drugs.

Complete non-congenital AV block is an adverse effect of high doses of antimalarial drugs (chloroquine and hydroxychloroquine) or prolonged treatment (40).

Other immunosuppressants

Azathioprine, cyclophosphamide and tacrolimus have adverse effects on lipid metabolism. Azathioprine has hepatic toxicity and may induce a fatty liver and elevate VLDL. The LUMINA cohort study associated this drug with a hazard ratio (HR) of 1.45 for arterial diseases (84). Similar results were presented by Doria *et al.* (85), but with no statistical significance. This association is currently being discussed and has led to confusion because patients undergoing azathioprine treatment have higher lupus activity.

Finally, cytotoxic drugs, especially cyclophosphamide, increase LDL cholesterol and predispose patients to accelerated atherosclerosis. However, this is considered a residual effect (86). Cyclophosphamide has a dose-independent cardiotoxic effect.

CONCLUSIONS

Systemic lupus erythematosus is an inflammatory autoimmune disease that frequently affects the heart. This involvement is mediated by immune deposits, persistent inflammation and autoantibodies. Pericarditis, myocarditis, heart valve disease, cardiac conduction system failure and, especially, accelerated atherosclerosis must be considered in SLE patients to identify disorders, order appropriate laboratory studies and initiate a specific treatment.

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