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Case report

Positive anti-Ro in lupus myocarditis: A case series report

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ABSTRACT

Cardiac involvement due to myocarditis in patients with systemic lupus erythematosus is rare; it is a severe clinical finding within the spectrum of the disease and may be the first manifestation of it. Timely diagnosis is crucial for the prognosis of the disease, based on fundamental clinical, biochemical/serological and imaging criteria to establish aggressive treatment to control the disease and secondary complications. Recognition of anti-Ro antibody positivity in myocarditis has been described, but little studied, with uncertainty about a causal association. Two clinical cases are presented, of patients who debuted with myocardial involvement and significant elevation of anti-Ro.

Anti-Ro positivo en miocarditis lúpica: reporte de serie de casos

Palabras clave:
Miocarditis
Lupus eritematoso sistémico
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RESUMEN

La miocarditis, hallazgo clínico poco frecuente en pacientes con lupus eritematoso sistémico, se relaciona con una mayor severidad y un peor pronóstico de la enfermedad, y puede ser su primera manifestación. El diagnóstico, sustentado en criterios clínicos, imagenológicos y bioquímicos, es una indicación para instaurar un tratamiento inmunomodulador temprano y probablemente de mayor intensidad. La positividad de anticuerpos anti-Ro en miocarditis lúpica ha sido descrita, pero se le ha estudiado poco, de

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manera tal que hay incertidumbre en torno a una asociación causal. Se presentan 2 casos clínicos de pacientes que comenzaron con compromiso miocárdico y elevación importante en los títulos de anti-Ro.

Introduction

Cardiac involvement by systemic lupus erythematosus (SLE) can be found in up to half of diagnosed patients, with affection described in the pericardium, myocardium, valve tissue, and coronary arteries. Lupus myocarditis is a severe clinical manifestation and can present early in the disease or late in the natural history, especially in subjects who do not receive optimal immunosuppressive treatment.[1] It is defined as a combination of symptoms and new or worsening changes in echocardiographic or cardiac magnetic resonance imaging (CMR) findings, including new wall motion abnormalities, left ventricular (LV) ejection fraction less than 45%, deterioration of LV function, and late gadolinium enhancement on CMR in an epicardial-myocardial pattern, all this in patients without a history of coronary heart disease.[2]

The diverse clinical presentation manifests with dyspnea of varying degrees, fatigue, chest pain, or palpitations. The clinical picture associated with the positivity of biomarkers, as well as the suggestive findings in the echocardiogram and CMR, reliably support the diagnosis.[3] Endomyocardial biopsy,[4] of limited use, has low sensitivity and can be associated with severe complications such as cardiac tamponade, atrioventricular block requiring a permanent pacemaker, pericardial effusion, and cardiac conduction abnormalities.[5]

The association between high titers of anti-Ro antibodies and lupus myocarditis remains unknown, despite multiple reports that suggest it.[6] Anti-Ro antibodies react against an intracellular ribonucleoprotein called Ro (Ro RNP), of 52 and 60 kDa and cytoplasmic RNA.[7] They are present in 30%–50% of individuals diagnosed with SLE.[8] In newborns, an arrhythmogenic potential associated with the development of congenital heart block and neonatal lupus has been described; however, its role in the adult patient is still uncertain,[9] although conduction disorders, ventricular arrhythmias, and QT prolongation have been described.[6,10,11]

Two cases of patients who began with cardiac involvement due to lupus associated with positive anti-Ro titers are presented.

Case presentation

Case 1

An 18-year-old female patient was admitted to the emergency department due to a 3-month clinical picture of fever, asthenia, adynamia, dark urine with foam, lower limb edema, and arterial hypertension in the last month, confirmed by ambulatory blood pressure monitoring (ABPM), difficult to treat despite angiotensin 2 receptor antagonists and thiazide. The patient did not report underlying diseases, and she had a puerperium in the previous 6 months, without complications. She also did not report a family history of cancer or autoimmune diseases. In the physical examination on admission, she was pale, with BP: 179/115 mmHg, HR: 93 bpm, RR: 19 rpm, SaO_2: 100% at room air, neck without jugular venous distention, and lower extremities with grade I pitting edema. She had no oral or nasal ulcers, alopecia, capillary fragility, malar erythema, synovitis, or skin lesions, while the neurological, cardiopulmonary, and abdominal examinations were unremarkable (the laboratory studies are reported in Table 1).

A diagnosis of SLE was performed, according to clinical and immunological criteria, with moderate activity according to SLEDAI-2K (11 points); hence, intravenous pulses of methylprednisolone for 5 days at a dose of 500 mg/day and intravenous cyclophosphamide 500 mg were started.

During hospitalization, the patient presented orthopnea and lower limb grade II pitting edema. When she was questioned again, she reported dyspnea on moderate exertion in the last 2 months. Chest X-rays depicted an increase in the cardiomediastinal silhouette without pleural effusion and a transthoracic echocardiogram reported mild eccentric LV hypertrophy, global decrease in contractility, segmental abnormalities predominantly in the interventricular septum and anterior wall, ejection fraction of 47%, mild mitral valve and left atrial dilation, and a PASP of 60 mmHg. Baseline pro-BNP was 11,674 pg/m and troponin T was negative. The electrocardiogram showed sinus rhythm, HR of 80 bpm, anterolateral early repolarization disorder, without dynamic changes in the ST segment, and the 24-h Holter without rhythm alterations. She was assessed by cardiology, optimizing treatment for acutely decompensated heart failure; a follow-up transthoracic echocardiogram was performed at 10 days, which did not report significant changes compared to the first study; control pro-BNP control was 16.463 pg/m.

After 19 days and an improvement in renal function, CMR was performed, which documented an LV infiltrative process consistent with lupus myocarditis. The patient continued immunosuppressive treatment with intravenous cyclophosphamide, a monthly dose of 500 mg for 6 months.

Case 2

A 50-year-old female patient who consulted due to a 2-day clinical picture consisting of asthenia, adynamia, and sudden dyspnea accompanied by oppressive precordial chest pain, radiating to the dorsal region occurring at rest. Four months before admission, she presented evening lower limb edema and orthopnea. In the systems review, she reported alopecia, oral ulcers, and non-specific joint pain in the upper limbs. She

Table 1 – Report of lab tests and serologies of the patients during the hospital stay.

Paraclinical	Case 1	Case 2
Leukocytes (K/ul)	4.99	5.78
Lymphocytes	2.0	1.9
Hb (g/dl)	7.3	10.6
Hematocrit (%)	22.5	33
MCV (fl)	82	78.2
Platelets (×103/ul)	157.0	194
Creatinine (mg/dl)	2.43	1.45
BUN (mg/dl)	38.9	39.6
Albumin (g/dl)	2.57	2.02
HIV	Negative	Negative
VDRL (DLS)	Negative	Negative
HBsAg	Negative	Negative
Anti-HCV	Negative	Negative
FTA-Abs		
LDH (U/l)	318	
Haptoglobin (mg/dl; RR 30–200)	3.0	
Prothrombin time (s)	11.4	12.3
Thromboplastin time (s)	22.5	25.2
HbA1C (%)		5.4
TSH (uUI)	3.69	7.20
FT4 (ng/dl)	0.95	1.12
LDL-C (mg/dl)		123
Total cholesterol (mg/dl)		195
HDL-C (mg/dl)		31.1
Triglycerides (mg/dl)		202
Urinalysis	Proteinuria 75 mg/dl, hematuria 250 ery	pH: 5.00 proteinuria 150 mg/d, hematuria 250 ery
24-h proteinuria (g)	1.0	2.5
Complement (C3) (mg/d; RV 90–180)	16.70	17
Complement (C4) (mg/d; RV 10–40)	2.90	4.8
Direct coombs	Positive (1+)	Positive (3+)
Peripheral blood smear	No schistocytes	No schistocytes
Anti-Ro (MPL U/ml)	+124.25	+137.03
Anti-La (GPL U/ml)	+24.31	+27.57
ANA	+1/1,280	+1/640
	Homogeneous pattern	Homogeneous pattern
NT-pro BNP (pg/m)	11,674	9,903

HBsAg: hepatitis B surface antigen; ANA: antinuclear antibodies; BUN: blood urea nitrogen; HDL-C: high density cholesterol; LDL-C: low density cholesterol; DLS: dilutions; FTA-Abs: fluorescent treponemal antibody test; GPL: IgG phospholipids; HCV: hepatitis C virus; Hb: hemoglobin; Hct: hematocrit; LDH: lactic dehydrogenase; MPL: IgM phospholipids; TSH: thyroid stimulating hormone; MCV: mean corpuscular volume; VDRL: Venereal Disease Research Laboratory; HIV: human immunodeficiency virus; FT4: free T4; RR: reference range.
Source: self-made.

had a history of arterial hypertension on treatment with losartan, nifedipine, and hydrochlorothiazide, along with chronic kidney disease of unknown etiology, diagnosed the previous year, and subclinical hypothyroidism.

The physical examination on admission showed BP: 110/60 mmHg, HR: 110 bpm, RR: 20 rpm, SaO_2: 93% at room air, afebrile, neck without jugular venous distention, and extremities with grade II pitting edema. Neurological, cardiopulmonary, and abdominal examinations were normal (laboratory studies are reported in Table 1).

The electrocardiogram showed repolarization disorder in the anterolateral wall and occasional ventricular extrasystoles, while a weakly positive troponin value with a negative delta was found. Transthoracic echocardiogram demonstrated slightly dilated LV, with a discrete decrease in overall contractility, an ejection fraction of 45%, and mild pericardial effusion, with no hemodynamic repercussions. Left heart catheterization reported coronary arteries without obstructive atherosclerotic disease. Due to persistent dyspnea of mixed origin and positive D-dimer (6.43 μg/m), ventilation/perfusion scintigraphy was performed, which confirmed acute pulmonary thromboembolism; pro-BNP value was 9.903 pg/m.

Because she was a young patient with an arterial thrombotic event, cardiac and renal involvement, an autoimmune disease was suspected. Antinuclear antibodies (ANA) (1/640 homogeneous pattern), anti-Ro (137.03 U), anti-La (27.57 U), anti-RNP (26.6 U), lupus anticoagulant, and anti-cardiolipin IgM (>12 MLP U/ml measured by enzyme immunoassay (EIA), and rheumatoid factor (32 UI/m) were all positive; anti-Sm, anticardiolipin IgG, and anti-b2 glycoprotein IgG and IgM antibodies were negative.

A diagnosis of SLE was confirmed, sustained on renal and hematological involvement, polyserositis, complement consumption, positive direct Coombs and ANA; joint affection with Jaccoud's arthropathy predominantly in the right hand; oral and nasal ulcers, as well as non-scarring alopecia. The disease activity was high, (SLEDAI-2K score of 15 points), associated with secondary antiphospholipid syndrome and

Table 2 – Summary of clinical and imaging characteristics of the patients.

	Case 1	case 2
CM	RPGN CHF Hypertensive crisis	Chest pain CHF Nephritic syndrome
SLEDAI-2K	Moderate activity (11 points)	High activity (15 points)
Troponins	Negative	Negative
EKG	Anterolateral early repolarization disorder	Anterolateral wall repolarization disorder and occasional ventricular extrasystoles
ECG	Global decrease in contractility and segmental alterations, predominantly in the interventricular septum and in the anterior wall, EF = 47%	Mild decrease in global contractility, mild involvement of systolic function EF = 45%, mild pericardial effusion
CMR	Infiltrative process in the left ventricle	Increased and heterogeneous enhancement of the myocardium of LV, RV, and septum; late enhancement in intramyocardial patches of the LV RV, and pericardium
LHC	Not performed	Normal

LHC: left heart catheterization; ECG: echocardiogram; EKG: electrocardiogram; EF: ejection fraction; RPGN: rapidly progressive glomerulonephritis; CHF: congestive heart failure; CM: clinical manifestations; CMR: cardiac magnetic resonance; LV: left ventricle; RV: right ventricle.
Source: self-made.

high suspicion of lupus myocarditis, for which management was started with intravenous pulses of methylprednisolone 500 mg × 3 days. In addition, hydroxychloroquine, mycophenolate mofetil –with titrated doses up to 3 g per day–, and anticoagulation with low molecular weight heparin were initiated, initially with subsequent adjustment to warfarin.

During hospitalization, a renal biopsy was performed, which confirmed ISN/RPS lupus nephritis with a mixed pattern: classes II and V.

Cardiac magnetic resonance was requested, in which increased enhancement of the myocardium was found in both ventricles and the septum, in the early perfusion sequences; in the late images, an intramyocardial patchy enhancement was observed in the apex, portion of the base of the LV and part of the RV, along with global dysfunction of LV motility, which confirmed lupus myopericarditis; treatment was adjusted to azathioprine 125 mg/day due to intolerance to mycophenolate mofetil.

Table 2 presents a summary of the clinical and imaging characteristics of the patients.

Discussion

Lupus myocarditis is a rare manifestation in patients with SLE, which is associated with greater severity of the disease and may be its initial presentation. It is crucial to make an early diagnosis and optimal treatment to improve prognosis.[12,13] Myocardial, valvular, and coronary vascular injury is mediated by immune complexes, with fine granular deposits demonstrated by direct immunofluorescence.[14] Some reports have documented an association between the presence of circulating anti-Ro antibodies and the development of myocarditis and cardiac conduction disorders[15]; however, there is still no evidence to explain a direct causal effect. The diagnosis of lupus myocarditis is based on the presence of clinical manifestations, positivity in biomarkers, and imaging findings; endomyocardial biopsy remains the gold standard, although it is not done routinely in all subjects.[4,12]

In the current case series, the patients exhibited wide variability of clinical manifestations associated with autoimmune disease; renal involvement was common at the beginning of the disease, and cardiac affection not attributable to another etiology was demonstrated. In both cases, an alteration in global cardiac contractility with deterioration of the ejection fraction was demonstrated. These findings have already been reported in previous series in individuals who begin with lupus myocarditis and are present in 69% and 41%, respectively.[13] The echocardiographic finding of global myocardial hypokinesia in subjects with SLE without evidence of coronary heart disease (CHD) supports the diagnosis of lupus myocarditis.[1]

A common feature in these cases is the presence of troponins in the normal range, with significantly elevated NT-pro BNP values related to acutely decompensated heart failure, a form of presentation previously reported,[1,3,14,16,17] but contrary to what was reported by Thomas et al., who recorded elevation of troponins in up to 80% of cases.[13] CMR is an important diagnostic tool in cases in which myocarditis is suspected. In this case series, it could be performed in the 2 patients, and findings of late gadolinium enhancement and LV infiltration were documented that are consistent with myocarditis.[14,15]

The serological findings of the individuals with lupus myocarditis are variable; in all cases ANA were positive, and, like Rovenský and Tuchynová,[15] one of the patients presented positive anti-RNP in a weak titer and met criteria for antiphospholipid syndrome. The anti-Ro antibodies were positive in both cases, being positive in high titers.

In patients with lupus myocarditis, a significant elevation in anti-Ro serum levels occurs in 36%–53% of cases.[13,15] There is a hypothesis that there may be a direct causal relationship between anti-Ro antibodies and myocardial injury in adult patients with SLE, an association more widely described in neonatal lupus; nonetheless, there are no studies that allow us to find this causal relationship. The current publication hopes

to motivate future studies to confirm this hypothesis. Until then, in daily clinical practice, the finding of positive anti-Ro antibodies in subjects with SLE should alert to the possibility of cardiac involvement.

Conclusion

There is a significant percentage of patients with SLE who present positivity for anti-Ro antibodies and manifestations of heart disease, including myocardial affection; therefore, it is necessary to expand the studies that allow the assessment of causal associations to define risk groups and interventions that prevent the development of cardiac complications in this group of patients.

Ethical responsibilities

This case report was performed with the informed consent of the patients, according to resolution No. 8.430 of 1993 of the Colombian Ministry of Health, which guarantees the confidentiality of patient data, following the principles of the Declaration of Helsinki. Participants in this research were only people of legal age according to Colombian legislation, from whom written informed consent was obtained for the collection of information, data analysis, and publication of the results, maintaining their anonymity throughout the process.

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Conflict of interests

The authors of this case report have no conflict of interest concerning the preparation of the manuscript.

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