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Endomyocardial biopsies in the diagnosis of myocardial involvement in systemic lupus erythematosus

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Abstract

Background: Endomyocardial biopsy (EMB) is considered the gold standard for diagnosing myocardial involvement in most inflammatory conditions, including systemic lupus erythematosus (SLE). However, EMBs are rarely performed, and most of the myocardial histopathology reports in SLE consist of postmortem data. We therefore sought to describe the histopathologic findings of contemporary EMBs in SLE performed in clinical practice.

Methods: A retrospective review of histopathology reports from SLE patients who underwent EMB from 1994 to 2017 was performed. A total of 41 SLE patients had cardiac pathology reports. Of these, 11 histopathology reports were EMBs, and the remaining were valvular specimens.

Results: A total of 11 SLE EMBs were reviewed. It was found that 45% of the patients had hypertension, 27% had coronary artery disease, 9% had hyperlipidemia, and 36% had end-stage renal disease. None had diabetes or smoked. The mean left ventricular ejection fraction was 37%. On histopathology, 10 had mild interstitial fibrosis, 9 had myocyte hypertrophy, 3 had organized blood clots, and 3 had a mild infiltration of lymphocytes and macrophages without clear evidence of myocarditis. None had vasculitis, endocarditis, ischemia, amyloid deposition, or lamellar or curvilinear inclusions.

Conclusion: EMBs are rarely performed in SLE. In this case series, nonspecific interstitial fibrosis and myocyte hypertrophy were the most common findings, suggesting EMBs have limited value in the diagnosis of cardiac involvement in SLE and rather rule out competing conditions. These data support the need for diagnostic methods with high sensitivity and specificity for SLE heart disease. *Lupus* (2020) **29**, 199–204.

Keywords

Endomyocardial biopsy; SLE; myocarditis

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Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder, predominantly affecting young women, characterized by autoantibody production, inflammation, and tissue injury that results in clinical disease manifestations. Cardiac involvement occurs in >50% of SLE patients, and every structure of the heart can be affected.¹ While little is known about lupus myocarditis, it is thought to be an immune complex-mediated process that leads to complement activation, inflammation, and myocardial injury, with a subclinical prevalence reported as high as 80% in early postmortem studies.^{2,3}

Diagnosing lupus myocarditis can be challenging, as it relies on clinical symptoms and electrocardiographic abnormalities that lack specificity. Endomyocardial biopsy (EMB) is the gold standard for determining myocardial involvement, with the finding of an inflammatory infiltrate in association with myocyte degeneration supportive of the diagnosis.^{3,4} Most of the myocardial histopathology reports in the literature consist of postmortem data prior to the introduction of disease-modifying agents.^{2,3,5,6} In a more recent study, Mavrogeni and colleagues described results of EMBs performed in seven SLE patients with clinical and cardiac magnetic resonance (CMR) findings suggestive of lupus myocarditis; only three of these seven cases had immunohistology suggestive of myocarditis.⁷ Nowadays, EMBs are rarely performed in clinical practice due to procedural risk and the low yield that results from sampling only the right ventricle, whereas predominantly left ventricular (LV) involvement is seen on imaging of lupus myocarditis.⁸ We therefore sought to describe the histopathologic findings of EMBs from SLE patients identified from the database of a large cardiology care center.

Methods

Patients

SLE patients aged 18 years who underwent EMB at Columbia University from 1994 to 2017 were retrospectively studied. We queried the New York-Presbyterian/Columbia University hospital data warehouse for the diagnosis of SLE identified by ICD-9 and –10 codes. EMBs were similarly identified by procedure codes for cardiac pathology. Out of 1994 SLE patients identified, 59 had cardiac pathology reports. Of the 59 cases, the diagnosis of SLE was confirmed in 41 patients by manual chart review based on four or more revised 1997 American College of Rheumatology or Systemic Lupus International Collaborating Clinics classification criteria for SLE.^{9,10} A total of 11 histopathology reports were EMBs and are included in this report; the remaining corresponded to valvular specimens. The study was approved by the Columbia University Institution Review Board.

Histopathology

Histopathologic reports of sectioned blocks of cardiac tissue were reviewed. Light microscopy results of hematoxylin and eosin staining were ascertained for presence of inflammatory infiltrate, vasculopathy, or endocardial disease. Masson trichrome staining was described for the presence and extent of fibrosis. Results of special iron stain for hemosiderin and Congo red and crystal violet stains for amyloid were recorded, and the

electron microscopy evaluation was reviewed for the presence of lamellar or curvilinear inclusions.

Clinical covariates

Demographics, comorbidities, smoking history, and medication at the time of the EMB were ascertained from review of electronic medical records. Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or antihypertensive medication use. Diabetes was defined as glycosylated hemoglobin (HbA1c) $>6.4\%$ or use of diabetes medication. SLE disease duration was defined as the duration in years from the date of physician diagnosis.

Laboratory covariates

Laboratory covariates, including troponin, anti-dsDNA, C3, C4, anti-Ro/SSA, anti-La/SSB, anti-Sm, anti-RNP, and antiphospholipid (aPL) antibodies, were ascertained from the clinical charts.

Cardiac covariates

Measures of ventricular function just prior to the EMB were recorded from transthoracic echocardiographic reports for all patients. LV function was assessed by the ejection fraction (LVEF) percentage. LV dilatation was defined as a LV end-diastolic dimension >6.0 cm for men or >5.4 cm for women. LV hypertrophy (LVH) was defined as concentric wall thickness >13 mm. Hemodynamic measurements of pulmonary artery pressure, capillary wedge pressure, and cardiac output were obtained from right heart catheterizations performed on the day of the EMB. Evaluation for presence of ischemic heart disease was based on results of left heart catheterization or cardiac stress testing. None of the patients had CMR or (18)F-fluorodeoxyglucose positron emission tomography (FDG-PET) data available prior to the EMB.

Statistical analysis

Baseline characteristics were summarized as the mean $\pm$ standard deviation or median and interquartile range (IQR). Counts and percentages are reported for categorical variables. Histopathological findings were analyzed as a dichotomous variable defined by the presence of each specific histological feature of interest. Univariate analyses were performed using the Mann–Whitney *U*-test (for continuous data) and Fisher's exact test (for categorical data). An alpha of 0.05 was defined as statistically significant. All statistical calculations were performed in Stata IC v15.1 (StataCorp, College Station, TX).

Results

Patient characteristics

The demographics and disease characteristics of the patients are summarized in Table 1. The mean age was 37 ± 17 years; 82% were female, and median disease duration was 2.5 years (IQR 0–25 years). Anti-ds-DNA and anti-Ro/SSA antibodies were present in 64% and 45% of cases, respectively. A total of 45% had hypertension, 18% had a history of coronary artery

disease, 9% had hyperlipidemia, and 36% had end-stage renal disease, while none had diabetes or smoked. Just one patient had a history of aPL syndrome and was on chronic anticoagulation.

Clinical presentation

The indication for EMB was a non-ischemic cardiomyopathy with declining LV function in all but one patient; the latter had echocardiographic findings of regional wall motion abnormalities and a recurrent pericardial effusion, despite pericardiocentesis and corticosteroid therapy. The reduction in the LVEF was mild (40–49%) in two patients and moderate-severe (<40%) in the others. In total, seven of the patients had a diagnosis of SLE that predated the cardiac symptoms; five of these patients were on immunosuppressive therapy. Dilated cardiomyopathy was the presenting symptom that led to the diagnosis of SLE in the remaining four patients. Of these, two patients developed symptoms postpartum, and one after an upper respiratory tract infection.

Cardiac measurements

All patients had a transthoracic echo and nine had a right cardiac catheterization performed prior to the EMB (Table 1). A pericardial effusion was present in six patients. The mean estimated LVEF was $30 \pm 17\%$. LV dilatation and LVH were present in seven (64%) and five (45%) of the patients, respectively. Right ventricular dysfunction was present in nine (82%) of the patients. The resting mean pulmonary artery systolic pressure was 25mm Hg in three of the patients, with mean pulmonary capillary wedge pressure 15mm Hg present in two, suggesting left-sided heart disease as the source of the pulmonary hypertension.

Troponin levels were elevated in two patients ($M=0.15$ ng/ml). A total of seven patients underwent coronary artery evaluation and/or cardiac stress testing, which ruled out obstructive ischemic disease as the cause of the declining LVEF. The remaining four patients did not undergo these tests per the discretion of the treating physicians that considered ischemic heart disease unlikely.

Histopathology results

All EMBs were obtained from the right ventricle as per conventional practice. On light microscopy, myocyte hypertrophy was seen in nine (82%) of the patients (Figure 1(a)); 10 (91%) of the patients had mild interstitial fibrosis on trichrome stain; three (27%) had organized blood clots, and another three (27%) had a mild infiltration of lymphocytes and macrophages (Figure 1(b) and (c)). The latter was interpreted by the pathologists as nonspecific for myocarditis and consistent with a cardiomyopathy of undetermined etiology. None of the patients had vasculitis, ischemic features, endocarditis, iron storage disease, or amyloid deposition. Vacuolization of myocytes with glycogen aggregates, compatible with glycogen storage disease, was observed in one patient who was simultaneously receiving treatment for lupus nephritis. No lamellar or curvilinear inclusion bodies were identified on electron microscopy.

Clinical predictors of cardiac inflammation

There was a trend toward having both anti-Ro/SSA and anti-La/SSB positivity in patients with an active inflammatory infiltrate on EMB. However, this was not statistically significant (67% versus 13%; $p=0.08$). No significant association was noted between the clinical, laboratory, or echocardiograph covariates and EMB findings.

Discussion

This study looked at a series of EMBs in SLE patients with suspected myocarditis without ischemic heart disease identified from a large cardiac care center patient population. Interstitial fibrosis and myocyte hypertrophy were the most common findings, and only three patients had evidence of a myocardial inflammatory infiltrate. No antimalarial cardiotoxicity was seen in any of the four patients on chronic antimalarial therapy.

Any structure of the heart can be affected in SLE.¹ While clinically evident myocarditis is considered an uncommon manifestation of SLE, its complications can be serious and can include cardiac conduction abnormalities, cardiomyopathy with heart failure, and sudden cardiac death.¹¹ Prompt diagnosis is essential yet challenging, as it relies on nonspecific symptoms and clinical tests. Histopathology is considered necessary to establish the diagnosis, and guidelines recommend EMB in all patients presenting with a newly depressed EF without a known etiology.⁴ However, EMBs are rarely performed in clinical practice due to the invasive nature of the procedure and potential risks, which limit the biopsy site to the right ventricle, resulting in a lower yield, as it is the LV that is predominantly affected in FDG-PET studies of lupus myocarditis.⁸ In this series of EMBs in suspected SLE myocarditis patients, only 27% had evidence of an inflammatory myocardial infiltrate, and these were considered to be nonspecific for myocarditis. These findings suggest that EMBs have limited value in the diagnosis of lupus myocarditis and are instead more useful to rule out alternative diagnoses.

Reports of histologic findings in lupus myocarditis are mostly based on postmortem studies published before the 1980s. In necropsy studies from the 1950s and 1960s, prior to the regular use of immunosuppressive therapy, focal interstitial myocardial inflammatory cell infiltrates were noted in 40–80% of SLE patients.² In 1975, Bulkley and colleagues reported a decreased frequency in myocardial interstitial inflammation (present in only 8% of patients) in 36 corticosteroid-treated SLE patients.⁶ Subsequent reports describe 60–80% prevalence of cardiac fibrosis and LVH on autopsies in SLE, with evidence of myocarditis present in <30% of EMB specimens.^{5,12} Similarly, Mavrogeni and colleagues found the sensitivity of EMB to detect myocarditis to be <50% in SLE patients with clinical and CMR findings consistent with lupus myocarditis.⁷ The compilation of these previous studies and our EMB findings raise concern for EMB not being the optimal clinical tool for the diagnosis of lupus myocarditis.^{5,7,12}

A trend toward anti-Ro/SSA and anti-La/SSB positivity was noted in patients with an active inflammatory infiltrate, but our sample size was underpowered to detect a statistically significant difference. While the association of maternal anti-Ro/SSA and anti-La/SSB antibodies with congenital heart block is well accepted,¹³ the role of these autoantibodies in

adult myocardial involvement in SLE is less clear. However, similar to our findings, the association between these antibodies and the presence of myocarditis and conduction defects in adults with SLE has been described.^{14,15}

Our study is limited by a small sample size. Yet, it is, to our knowledge, the largest case series of EMBs from the last decade. Importantly, the disquieting lack of specific findings on the EMB in all of the specimens was consistent with results reported by other groups.^{7,12,16} In addition, though the distribution of positive immunofluorescence does not always correlate with sites of myocardial inflammation and is instead more strongly associated with findings of pericarditis or valvulitis,⁵ direct immunofluorescent studies were not performed in our EMB series. In addition, four of the patients in the series lacked definitive cardiac testing for ischemic heart disease, although both the absence of anginal symptoms and the lack of ischemic findings on histopathology suggest that ischemic disease was not the cause of their declining LV function. Finally, our EMBs are limited to the right ventricle. However, this is the universally accepted biopsy site in EMBs, given the high risk associated with LV biopsies.⁴

In conclusion, we found nonspecific interstitial fibrosis and myocyte hypertrophy to be the most common findings on EMBs from SLE patients with suspected lupus myocarditis. Although considered the gold standard, EMBs may have limited value in the diagnosis of myocardial involvement in SLE. As a result, noninvasive imaging modalities such as CMR and FDG-PET are recently being favored in clinical practice. CMR allows for the detection of myocardial inflammation with 81% sensitivity, and up to 90% when using T1 mapping techniques that detect focal areas of myocardial edema and/or fibrosis.¹⁷ Similarly, FDG-PET enables visualization of tissues with increased metabolic activity that underlies regional inflammation. Future studies using FDG-PET/CMR hold promise for an improved alternative for evaluation of myocardial involvement in SLE.

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Figure 1. Histopathology findings from one patient with clinically suspected systemic lupus erythematosus myocarditis. (a) Light microscopy shows myocyte hypertrophy with a small amount of interstitial fibrosis. (b) and (c) Scant CD68- and CD3-positive staining consistent with mild myocardial inflammatory infiltrate of macrophages and lymphocytes, respectively.

Table 1

Patient characteristics

	SLE (N=11)
Demographics	
Age (years), $M \pm SD$	38 $\pm$ 17
Female, n (%)	9 (82)
Race/ethnicity (N=7)	
Non-Hispanic white, n (%)	0
Non-Hispanic black, n (%)	2 (29)
Hispanic, n (%)	3 (43)
Asian, n (%)	2 (29)
SLE characteristics	
SLE duration (years), median (IQR)	2.5 (0–25.5)
Lupus nephritis, n (%)	5 (45)
End-stage renal disease, n (%)	4 (36)
Antiphospholipid antibody syndrome, n (%)	1 (9)
Antinuclear antibodies, n (%)	11 (100%)
Anti-ds-DNA, n (%)	7 (64)
Anti-Ro/SSA, n (%)	5 (45)
Anti-La/SSB, n (%)	3 (27)
Anti-Sm, n (%)	5 (45)
Anti-RNP, n (%)	5 (45)
Antimalarials, n (%)	4 (36)
Steroids, n (%)	4 (36)
Mycophenolate mofetil, n (%)	4 (36)
Azathioprine, n (%)	0
Methotrexate, n (%)	0
Cyclophosphamide, n (%)	0
B-cell targeting therapy, n (%)	0
Cardiovascular risk factors	
Smoking, n (%)	0
Hypertension, n (%)	5 (45)
Diabetes, n (%)	0
Hyperlipidemia, n (%)	1 (9)
Statin use, n (%)	3 (27)
Coronary artery disease, n (%)	2 (18)
Body mass index (kg/m^2), $M \pm SD$	21 $\pm$ 4
Transthoracic echocardiography	
LV ejection fraction (%), $M \pm SD$	30 $\pm$ 17
LV dilatation, n (%)	7 (64)
LV hypertrophy, n (%)	5 (45)
RV dysfunction ^a n (%)	9 (81)

	SLE (N=11)
Valvular abnormalities, <i>n</i> (%)	3 (27)
Pericardial effusion, <i>n</i> (%)	6 (55)
Trace	3
Moderate	3
Right heart catheterization (<i>n</i> =9)	
Cardiac index (L/min/m ²), <i>M</i> ± <i>SD</i>	2.8±0.7
Pulmonary artery systolic pressure, mean (mm Hg), <i>M</i> ± <i>SD</i>	23±10
Pulmonary capillary wedge pressure, mean (mm Hg), <i>M</i> ± <i>SD</i>	11±8

^aHypokinesis, dilation, or decreased systolic function.

SLE: system lupus erythematosus; *SD*: standard deviation; IQR: interquartile range; LV: left ventricular; RV: right ventricular.