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Editorial

Endomyocardial biopsy in myocarditis: need for proper tissue characterization to keep it alive and kicking

Biopsia endomiocárdica en la miocarditis. Necesidad de una correcta caracterización tisular para mantenerla viva

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«What you gonna do when things go wrong?
What you gonna do when it all cracks up?
What you gonna do when the love burns down?
What you gonna do when the flames go up?
Who is gonna come and turn the tide?
What's it gonna take to make a dream survive?
Who's got the touch to calm the storm inside?
Who's gonna save you?»

Alive and Kicking. Simple Minds, 1985

Myocarditis is an inflammatory disease of the heart that may develop following infections, exposure to toxic substances, and immune system activation.[1] The spectrum of clinical presentation is wide, from mild cases resolving spontaneously to sudden cardiac death or cardiogenic shock, or a persistent inflammation driving left ventricular (LV) remodeling.[1] From a clinical perspective, we can distinguish acute myocarditis (AM), chronic myocarditis and chronic inflammatory cardiomyopathy. In AM, the time from symptom onset to diagnosis is usually < 1 month. Chronic myocarditis is characterized by the persistence of myocardial inflammation, and chronic inflammatory cardiomyopathy also by a hypokinetic LV. Myocarditis can also be classified according to the cell infiltrates as lymphocytic, eosinophilic, giant cell, or granulomatous.[1]

Chest pain is the most frequent symptom of AM (85%-95%), followed by dyspnea (19%-49% of cases), whereas syncope occurs in about 6%.[2] Fever is common (about 65%), while other prodromal manifestations, such as flu-like symptoms, gastrointestinal disorders, sore throat, or respiratory tract infections, may precede the acute phase by a few days or weeks, with a prevalence ranging from 18% to 80%.[2] In a large series of patients with AM, 27% had a presentation complicated by LV systolic dysfunction, ventricular arrhythmias, or cardiogenic shock.[2]

Endomyocardial biopsy (EMB) may be crucial to define the etiology and decide the therapeutic strategy. A position statement by the European Society of Cardiology recommended that EMB be considered in "all patients with clinically suspected myocarditis",[3] while other documents have recommended EMB just in some specific settings.[1,4,5] A 2020 expert consensus document proposed the following indications to EMB: AM presenting with acute heart failure or cardiogenic shock, ventricular arrhythmias, or high-degree atrioventricular block; myocarditis in the setting of immune checkpoint inhibitor therapy; AM or chronic inflammatory cardiomyopathy associated with peripheral eosinophilia; AM or suspected chronic inflammatory cardiomyopathy with persistent/relapsing release of myocardial necrosis markers, especially if accompanied by suspected/known autoimmune disorders, ventricular arrhythmias or advanced atrioventricular block.[1] In these cases, the expected benefit from EMB overcomes the risk of cardiac complications (1%-2% at expert centers, but up to 9% at low-volume centers),[6] and the diagnostic yield is higher. EMB has a relatively low sensitivity as sampling sites do not always correspond to the sites of inflammation. Sensitivity may be increased by collecting at least 4 to 6 specimens, sampling both ventricles,[7] and/or using antibodies specific for leukocytes (CD45), macrophages (CD68), T cells (CD3) and their main subtypes, helper (CD4) and cytotoxic (CD8) cells, and B cells (CD19/CD20).[3] Quantitative criteria to improve the diagnostic yield of EMB include the Marburg criteria, requiring a clear-cut infiltrate (diffuse, focal, or confluent) of $>$ 14 leukocytes/mm^2 (preferably activated T cells) to diagnose AM.[8]

EMB is largely underused even in the recommended settings.[9] Furthermore, many open issues exist such as the interpretation of the extent and patterns of myocardial inflammation, the optimal use of viral panels, the application of novel technologies such as single-cell RNA sequencing, mass cytometry, T-cell receptor sequencing, multiplex immunofluorescence,[1] or -omic techniques.[10] Large-scale studies may be helpful to shed some light on some of these points.

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In a recent article published in *Revista Española de Cardiología*, Domínguez et al. analyzed all patients undergoing an EMB from 1997 to 2019 for suspected AM (n = 33) or chronic inflammatory cardiomyopathy (n = 66).[11] All these cases were evaluated through conventional histology. Immunohistochemistry was performed in an unspecified number of cases; the remaining cases were retrospectively analyzed for the purposes of this study. Myocarditis or chronic inflammatory cardiomyopathy was diagnosed in 28% of cases when the Dallas criteria were applied, and in 54% when immunohistochemistry was used (58% of patients with suspected AM, and 52% in patients with chronic inflammatory cardiomyopathy); only 3 cases of eosinophilic myocarditis met the Dallas criteria, but were negative to immunohistochemistry. The most common etiology (47% out of 54%) was lymphocytic myocarditis; 7% had only myocardial fibrosis, and as many as 36% had no pathological findings. Few complications were observed (2 perforations of the right ventricle [RV] requiring pericardiocentesis, 1 sustained ventricular tachycardia, and 1 transient ischemic attack), with no significant differences between biopsies performed in the RV or LV (4.4% vs 3.4%, respectively). As for complementary diagnostic techniques, viral polymerase chain reaction was employed in 38 patients, and cardiovascular magnetic resonance (CMR) was performed during the same month as EMB in 33 patients (with myocarditis diagnosed in 18 patients using immunohistochemistry, but only in 6 using the Lake Louise criteria for CMR interpretation). Patients with specific etiologies of myocarditis received immunosuppressive treatment. Over a median follow-up of 18 months, patients with immunohistochemistry-confirmed myocarditis tended to more frequently require heart transplant or LV assist devices, or died ($P = .056$). Patients with LV ejection fraction $\leq$ 30% or LV end-diastolic diameter $\leq$ 60 mm at baseline had a worse prognosis, especially when they had signs of myocardial inflammation on EMB.[11]

This is the largest cohort of patients undergoing EMB for suspected AM or chronic inflammatory cardiomyopathy in Spain so far,[11] and the authors should be congratulated for their efforts. A first message from this study is that the Dallas criteria, introduced in 1986,[12] are no longer sufficient to diagnose myocarditis in these patients. Back in 2006, an opinion article announced the "death of Dallas criteria" because of their limitations related to "sampling error, variation in expert interpretation, variance with other markers of viral infection and immune activation in the heart, and variance with treatment outcomes".[13] The Dallas criteria were to be replaced by a comprehensive approach including "immunohistochemistry, viral polymerase chain reaction, cardiac antibody assessment, and imaging results",[13] with the goal of diagnosing myocarditis and defining its etiology in a larger number of cases than with histology alone. Immunohistochemistry and molecular testing for viral detection were suggested in a 2011 document,[14] and recommended in all patients undergoing EMB in a 2013 position statement by the European Society of Cardiology.[3] The study period spanned from 1997 to 2019, and inevitably only a subgroup of EMBs were examined through immunohistochemistry or viral genome search at the time of diagnosis,[11] thus not affecting patient management. With this caveat, the association between evidence of myocardial inflammation and a higher risk of events (LV assist device, heart transplant, death) is plausible, and further stresses the importance of performing immunohistochemistry when AM or chronic inflammatory cardiomyopathy is suspected, to detect the presence of myocardial inflammation more reliably.

The percentage of patients with myocarditis not displaying a recovery in left ventricular ejection fraction or requiring heart transplantwas much lower than in a German cohort (37% vs 87%, respectively).[11,14] The most likely explanation is that referral to EMB was much more selective in the Spanish cohort.[11] This may reflect the widely different indications for EMB, from all patients with suspected myocarditis[3] to specific settings,[1,4,5] and may denote a crucial need to standardize the indications for EMB.

Patients in the Spanish cohort underwent EMB in the RV, LV, or both.[11] A study specifically focusing on the better site for EMB evaluated 755 patients referred to EMB (64% for suspected myocarditis) who underwent sampling of the LV, RV, or both ventricles according to the late gadolinium enhancement pattern on CMR. The rates of major complications were 0.64% of all LV biopsies, 0.82% of all RV biopsies, and 0.56% in the subgroup undergoing biopsy of both ventricles. Positive diagnostic EMB results were obtained significantly more often in those patients who underwent biventricular EMBs (79%), compared with those who underwent either selective LV-EMB or selective RV-EMB (both 67%; $P < .001$).[7] Notably, myocarditis was diagnosed in 73% of patients undergoing CMR, biventricular EMB, immunohistology and the search for viral genomes, compared with 54% in the Spanish cohort with stringent criteria for referral to EMB.[11] This further emphasizes the importance of thorough investigation of patients with suspected myocarditis, as discussed above.

A reliable assessment of the prognostic value of myocardial inflammation is complicated by the likely changes in patient referral policies and management strategies over a 22-year timespan, the retrospective diagnosis of myocarditis in some cases, the small number of events, and the pooled assessment of patients with acute or chronic disease.[11] Despite these possible limitations, reaching an etiological diagnosis has clear implications for therapy, thus possibly changing the natural history of the disease. Beyond the simple definition of the etiology, findings from classic (immuno)histological and virological analyses might refine risk prediction. As stated above, advanced techniques for tissue characterization (up to -omic technologies) might represent a further step forward.

In conclusion, the study by Domínguez et al.[11] provides important information on the use of EMB in patients with suspected myocarditis in a real-world setting. Beyond the specific results, which should be interpreted on the light of the retrospective design, this study prompts many considerations about the indications for EMB, the assessment of tissue samples, and the implications of EMB findings for outcome prediction and therapy.

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CONFLICTS OF INTEREST

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