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## Importance of endomyocardial biopsy in patients with myocarditis: A case report

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### Introduction

Endomyocardial biopsy (EMB) is an invasive diagnostic tool to clarify specific etiologies of dilated cardiomyopathy with unknown etiology and suspected infiltrative cardiomyopathy. Re-

cent case series indicate that EMB is a unique method for the diagnosis of myocarditis in >30% of unexplained cardiomyopathy cases (1). Differentiating specific types of myocarditis and infiltrative disease with EMB can lead to decide the appropriate therapy earlier and to improve the poor diagnosis of these diseases by this way. Based on the 2016 heart failure guidelines, EMB should be considered in individuals with rapidly progressive heart failure (HF) despite standard therapy, when there is a probability of a specific diagnosis which can be confirmed only in myocardial samples and specific treatment is available and effective (Class IIa and Level C).

### Case Report

A 28-year-old male patient presented to our emergency room with exertional dyspnea. His complaint existed 3 months ago and increased in time. There was no abnormal finding on his medical history and electrocardiogram. He had Class II HF symptoms and signs according to the New York Heart Association (NYHA). First, bolus intravenous loop diuretics and bronchodilator treatment via respiratory mask were applied. His transthoracic echocardiogram (TTE) examination revealed global hypokinetic left ventricular function. His left ventricular ejection fraction (LVEF), left ventricular global longitudinal strain (LV-GLS), and tricuspid annular plane systolic excursion were calculated as 26%, -6.8 cm, and 1.4, respectively (Video 1). He was hospitalized, and routine HF medication was given to the patient according to his monitoring and physical examination results. Coronary angiography demonstrated normal coronary artery flow. His peak pulmonary artery pressure was 60 mm Hg on TTE, and it was confirmed by right heart catheterization later. A 24-hour rhythm Holter examination showed short-term non-sustained ventricular tachycardia, and implantable cardioverter defibrillator implantation was planned. Despite ramipril 5 mg once a day, metoprolol 25 mg twice a day, spironolactone 50 mg once a day oral treatment, and furosemide 40 mg four times a day intravenous treatment, his HF symptoms were progressive. TTE and fluoroscopy-guided EMB were performed to diagnose the etiology of dilated cardiomyopathy. Nine cardiac biopsy specimens were obtained and sent to the Institut Kardiologie Diagnostik und Therapie center. Extensive inflammation without acute myocarditis was found. CD4 T cells, LFA-1 cells, and CD45RO were calculated as 14.43 mm<sup>2</sup> (>10 cells/mm<sup>2</sup>), 28.5 mm<sup>2</sup> (>14 cells/mm<sup>2</sup>), and 71.95 mm<sup>2</sup> (>40 cells/mm<sup>2</sup>), respectively. Before starting the immunosuppressive treatment, atrial fibrillation was revealed. After intravenous amiodarone 1200 mg treatment, oral medication was administered as 200 mg twice a day. After 10 days, his transaminase levels increased to 10 times due to amiodarone toxicity. A combination of prednisone 1 mg/kg/day tapered biweekly 10 mg and azathioprine 100 mg/day was started when transaminases decreased to normal range after amiodarone cessation. TTE was repeated on week 2 of treatment before discharge, and there was no remarkable

change. After 1 month, on his first outpatient control, his functional status was NYHA I, and his LVEF and LV-GLS were found to be 37% and  $-11.1$ , respectively (Video 2). Although steroid and azathioprine treatments were planned to taper in 6 months, azathioprine treatment was ceased according to hematological consultation because of severe anemia on month 3, whereas his LVEF was 37%, and GLS was  $-11.1$ . After 1 month in which he was just given guideline-directed medical treatment for HF and prednisolone 10 mg/day, LVEF was found to be 28%, and his functional status was worse (NYHA II). Our HF team decided on adding the anti-inflammatory treatment again, and cyclosporine 100 mg t.i.d. treatment was started. His TTE and physical examination results improved in just 1 month. LVEF and LV-GLS were calculated as 46.7% and  $-15.1$ , respectively (Video 3).

## Discussion

EMB is not routinely recommended to diagnose all cardiac disorders due to no randomized controlled treatment study exists on the utility of EMB. The American College of Cardiology/American Heart Association (ACC/AHA) recommends using EMB when the results can meaningfully estimate prognosis and guide the treatment. For this purpose, the ACC/AHA presents some scenarios in which EMB may be useful. According to these scenarios, when a patient has acute HF symptoms with hemodynamic compromise for  $<2$  weeks or HF symptoms exist for  $<3$  weeks, but heart blocks or new ventricular arrhythmias are accompanied, EMB is beneficial with Class I recommendation (2). In addition to these, EMB should be considered if a patient has HF symptoms accompanied with heart blocks or new ventricular arrhythmias  $>3$  weeks, rapidly progressive HF despite standard therapy, when there is a probability of a specific diagnosis which can be confirmed only in myocardial samples and specific treatment is available and effective (Class IIa and Level C), dilated cardiomyopathy suspected allergic etiology or anthracycline usage, unexplained restrictive cardiomyopathy, and cardiac tumors.

EMB provides the characterization of viral genomics, viral load, and type of inflammatory cells via histological, immunohistochemical, immunofluorescence, and viral diagnostics. The number of samples should range from 5 to 10, and each sample should be  $1-2 \text{ mm}^3$  in size. The sample must be handled carefully to minimize artifacts and transferred from the bioptome to the fixative (10% neutral buffered formalin) by the use of a sterile needle, and the fixative should be at room temperature [room temperature is taken to be about 20 to 25 degrees Celsius with an average of  $23 \text{ }^\circ\text{C}$  (about  $73.4 \text{ Fahrenheit } ^\circ\text{F}$ )] to prevent contraction band artifacts (3, 4). In addition, crush infarcts are possible during biopsy and can cause difficulties in pathological diagnosis.

Parvovirus B19 (B19V) and human herpes virus 6 (HHV6) are the most frequently found cardiotropic viruses in EMBs. These are followed by adenoviruses and enteroviruses (5). Previous tri-

als are suggesting that HHV6 and B19V can be bystander findings, and that ongoing inflammation is the main cause of outcomes. Therefore, viral myocarditis, in which the responsible agents are HHV6 and B19V, can respond to corticosteroid treatment similar to giant cell myocarditis, eosinophilic myocarditis, lymphocytic myocarditis, and hypersensitivity myocarditis. In contrast, the treatment must include specific antiviral treatment for adenoviruses and enteroviruses, and immunosuppressive treatment is contraindicated.

EMB may be appropriate if cardiac amyloidosis or Fabry disease is strongly suspected in a patient with hypertrophic cardiomyopathy. Primary amyloidosis is potentially responsive to chemotherapeutic agents or stem cell transplant, and Fabry disease may be responsive to enzyme replacement therapy (6, 7).

Most types of myocarditis are caused by maladaptive hyperimmune responses to infectious triggers. Therefore, several studies assessed the effect of immunomodulatory or immunosuppressive therapies in patients with EMB-proven myocarditis. Prednisone has been tested as monotherapy or in combination with other immunosuppressants. Prednisone monotherapy study found no significant differences of LVEF, NYHA functional class, inflammation of the myocardium, and number of clinical events in 15–24 months (8, 9). Mason et al. (10), Wojnicz et al. (6), and Frustaci et al. (7) investigated the effect of a combined treatment with an immunosuppressant (cyclosporine or azathioprine) plus prednisone for 3–6 months and found a significantly higher LVEF in the treatment group within the observational periods. Although not validated by robust randomized controlled data, this treatment approach has shown promising results in case series (11).

In addition, a meta-analysis of randomized controlled trials in regard to immunosuppressive treatment in myocarditis demonstrated that immunosuppressive treatment might be beneficial for improving left ventricular systolic function and remodeling in patients with myocarditis, which could be considered as a therapeutic alternative when optimal conventional therapy is not effective (12). Escher et al. (12) investigated 114 patients with EMB-proven virus-negative chronic myocarditis and showed the effectiveness and beneficial effects of immunosuppressive treatment based on the normalization of the inflammatory process. LVEF improvement lasts for a long-term follow-up period of up to 10 years (median 10.5 months).

Blood cardiac enzymes and inflammation parameters are nonspecific in the diagnosis and treatment of viral myocarditis. Although magnetic resonance imaging (MRI) can illustrate the areas of inflammation and fibrosis in myocarditis with technical advances, MRI is insufficient to identify the etiological viruses, to measure the viral load, and to detect the infiltrated immune cell subtypes. In our case report, we showed that only corticosteroid treatment can be ineffective in a lymphocyte-weighted myocarditis according to the subtypes of inflammatory cells, and that anti-inflammatory drugs can be mandatory.

## Conclusion

Differentiating specific types of myocarditis and infiltrative disease with EMB can lead to decide the appropriate therapy earlier and to improve the poor diagnosis of these diseases by this way. We demonstrated the importance of individualized therapy for myocarditis on this case study. Among patients with HF with suspected myocardial disease, EMB provides specific proof of subtypes of viruses, and inflammatory cells lead to start an aggressive treatment regime and improve the prognosis. Patients with circulating cardiac autoantibodies and no detectable viral genome or patients with human leukocyte antigen upregulation on EMB represent the response to immunosuppressive therapy. In the current case, deterioration of LVEF and functional status (FS) after the discontinuation of azathioprine therapy and enhancement of LVEF and FS after the start of cyclosporine therapy proved to us that myocardial inflammation can be treated by immunosuppressive therapy. However, there is a need for more randomized trial to assist with drug selection in this challenging group of patients.

**Informed consent:** Informed consent was obtained.

**Video 1.** First TTE video at admission.

**Video 2.** TTE video on second week of combination treatment with prednisone and azathioprine.

**Video 3.** Last TTE video on treatment of prednisone and cyclosporin.

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