

Giant cell myocarditis in an older patient – reassessing the threshold for endomyocardial biopsy

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Abstract

Giant cell myocarditis is a rare form of autoimmune myocarditis with high morbidity and mortality that affects mainly middle-aged adults. We report a case study of a 70-year-old man on chronic immunosuppression who presented with sustained ventricular tachycardia and symptoms of acute systolic heart failure, both with poor response to standard measures. A decision to pursue endomyocardial biopsy established the diagnosis of GCM and led to initiation of immunosuppressive therapy and a favourable outcome. Our case illustrates that a low threshold for endomyocardial biopsy in new onset heart failure can lead to actionable information even in patients of advanced age.

Keywords Endomyocardial biopsy; Giant cell myocarditis; Heart failure; Immunosuppressive treatment; Inflammatory heart disease

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Introduction

Giant cell myocarditis is a rare form of autoimmune myocarditis with high morbidity and mortality that affects mainly middle-aged adults. Most patients present with heart failure, ventricular tachyarrhythmias, heart block, or symptoms mimicking myocardial infarction. We describe a case of a 70-year-old white man who developed giant cell myocarditis despite his older age and chronic immunosuppression, and for whom an endomyocardial biopsy (EMBx) was paramount for establishing the correct diagnosis.

Case report

A 70-year-old U.S. tourist visiting the Czech Republic presented via emergency medical services to the General University Hospital in Prague with sudden onset of dizziness and palpitations. He had a past medical history of liver transplant for autoimmune hepatitis, chronic immunosuppression with everolimus and mycophenolate, ulcerative colitis, colorectal

carcinoma treated by total colectomy, and heart block with permanent dual-chamber pacemaker.

On admission, he was conscious and conversant. His vitals included blood pressure of 125/88 mmHg and pulse rate 200 bpm. Electrocardiogram showed ventricular tachycardia (VT) (Figure 1). Initial blood chemistries revealed elevated NT-proBNP (26 742 ng/l) and lactate (4,21 mmol/l) and mildly elevated liver enzymes. The patient soon became unstable, lost consciousness and required urgent electrical cardioversion, with a subsequent ECG showing an atrio-ventricular paced rhythm. However, recurrent sustained VTs of multiple morphologies resulted in progressive cardiogenic shock. Echocardiogram showed severely reduced bi-ventricular function with low cardiac output, and coronary angiography was unremarkable. He was placed on combined antiarrhythmic therapy consisting of amiodarone, propafenone, and mesocaine, and inotropic support with levosimendan.

Due to recurrent ventricular arrhythmias despite maximal medical therapy, urgent electrophysiological assessment and myocardial mapping was performed. Vast arrhythmogenic substrate was found mainly in the right ventricular free wall

Figure 1 ECG at admission showing sustained ventricular tachycardia of 200 bpm with LBBB morphology.



and right ventricular outflow tract (RVOT). Extensive radio-frequency (RF) ablation of all apparent foci was conducted (Figure 2). Rapid VT ceased, however a slower VT emerged several hours after the procedure.

Since the aetiology of the new onset heart failure and persistent ventricular arrhythmias was not clear, we pursued EMBx early in the clinical course. Light microscopy revealed large amount of inflammatory cellular infiltrate composed of lymphocytes, few eosinophils and neutrophils and several multinucleated giant cells, fibrosis, and necrotic myocytes. These findings were consistent with typical giant cell myocarditis (Figure 3). Immunohistochemistry showed predominance of CD68 positive histiocytes and a smaller number of CD3 lymphocytes.

The patient was started on high-dose methylprednisolone, tacrolimus and mycophenolate, and his everolimus was stopped. The malignant dysrhythmias abated and, once clinically stable, he was transferred to the University of Utah Hospital for continued management. Additional imaging studies performed once the patient's condition stabilized corroborated the diagnosis of giant cell myocarditis – cardiac magnetic resonance imaging showed multi-focal epicardial and mid-myocardial delayed gadolinium enhancement in both ventricles (Figure 4) and cardiac positron emission tomography showed patchy myocardial uptake (Figure 5). The patient remained with decreased left ventricle ejection fraction (LVEF), was started on a guideline-directed medical therapy

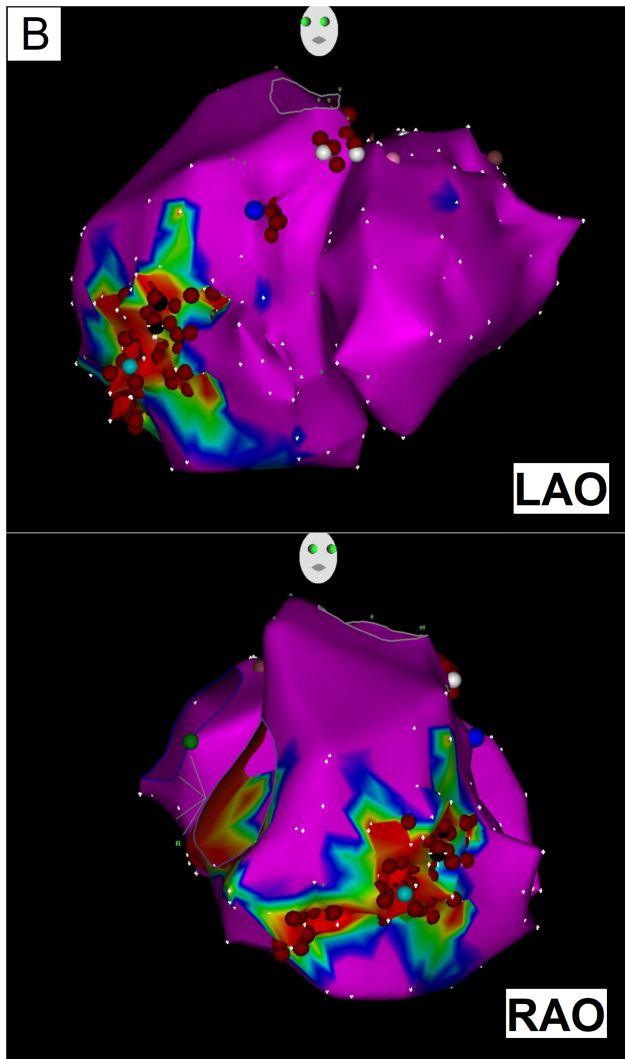
for new systolic heart failure, and his pacemaker was upgraded to cardiac resynchronization therapy/defibrillator (CRT-D).

One year after discharge, the patient was clinically stable with NYHA class II symptoms, and LVEF of 35% and mildly reduced right ventricular function by echocardiography.

Discussion

Giant cell myocarditis (GCM), first described by Saltykow in 1905,¹ is a rare and severe form of myocarditis with rapid progression that affects mainly middle-aged adults.² The prevalence on large autopsy studies has been reported at 0.007–0.053%.³ The exact aetiology remains unclear, but evidence suggests an important role of T lymphocytes leading to immune dysregulation.⁴ Most patients present with rapid-onset heart failure, ventricular tachyarrhythmias, heart block, or symptoms mimicking myocardial infarction.² There is no noninvasive assessment specific for GCM and histologic evaluation remains essential to establish the diagnosis.^{5–7} Immunosuppressive treatment is recommended, and regimens used have included a combination of calcineurin inhibitors, cell-cycle inhibitors, and steroids.⁸ Mechanical cardiac support or heart transplantation are often needed in patients

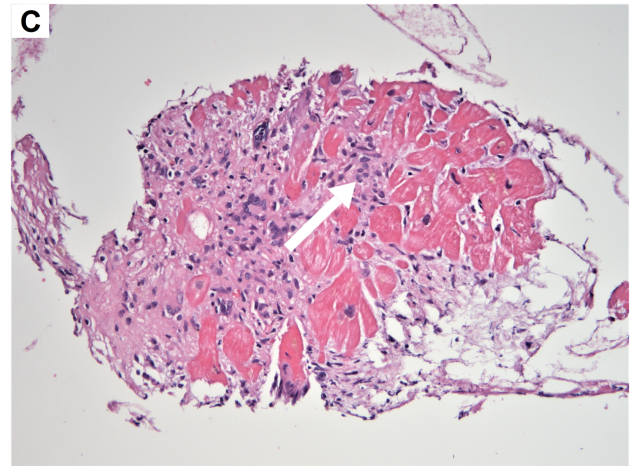
Figure 2 Voltage maps of left and right ventricles. Violet is healthy myocardium; blue to red represent arrhythmogenic substrate; red dots are ablation points; blue dot is tip of RV electrode.



with progressive heart failure symptoms unresponsive to immunosuppression.

Inclusion of GCM in the differential diagnosis of acute de novo onset of heart failure accompanied by VT is essential. A history of autoimmune disorders like ulcerative colitis and autoimmune hepatitis can be found in about 20% of patients with GCM,² which was probably a predisposing factor in our patient with history of autoimmune hepatitis. Ventricular arrhythmias can be found in 14–29% of patients with GCM,^{2,5} and radiofrequency ablation (RFA) has been successful as salvage therapy when incessant VT occurs.^{9,10} RFA in our patient provided temporary relief from VTs. Once EMBx-proven GCM was diagnosed and high dose steroids were initiated, the VT resolved completely.

Figure 3 Endomyocardial biopsy, haematoxylin and eosin stain, 200x magnification. Myocardium with extensive inflammatory cellular infiltrate with multinucleated giant cells (arrow), fibrosis, and necrotic myocytes.



Our case illustrates that EMBx can be an essential diagnostic tool even in situations where its use is not always considered, e.g. due to older patient age or a plausible alternative diagnosis. The AHA/ACCF/ESC Scientific Statement recommends use of EMBx in circumstances of new onset of systolic heart failure or electrical instability without a clear aetiology, as was the case in our patient.¹¹ However, there is often hesitancy to pursue the invasive EMBx because of concerns regarding complications, though the overall complication rates

Figure 4 Cardiac magnetic resonance imaging. Extensive, multi-focal epicardial and mid-myocardial delayed gadolinium enhancement involving the left ventricle and large segments of the right ventricular free wall (arrow) along with subendocardial enhancement of the right ventricular side of the ventricular septum.

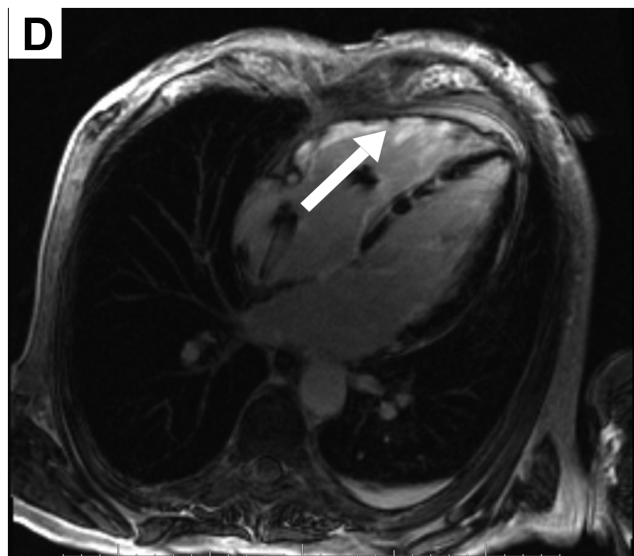


Figure 5 Cardiac positron emission tomography. Patchy areas of abnormal left ventricular uptake, particularly along the proximal inferior wall and septum (arrow).



reported across multiple case series are relatively low (1–6%).¹¹ Therefore, while step-wise, non-invasive testing can usually provide a diagnosis, the utility of EMBx should not be forgotten. In cases of acute systolic heart failure with

ventricular arrhythmias but no significant coronary artery disease, the differential diagnosis can be broad, and EMBx can identify or confirm diagnoses such as giant cell myocarditis, eosinophilic myocarditis, viral myocarditis or sarcoidosis. Early biopsies in these suspected cases can lead to changes in therapy and, in some cases, facilitate enrollment in clinical trials.¹² More liberal use of EMBx can also identify the currently greatly underdiagnosed patients with cardiac amyloidosis, for whom an expanding range of treatments are becoming available.¹³

In summary, our case is an example of the utility of EMBx in establishing the correct diagnosis in a patient with new onset heart failure and arrhythmia, and suggests it may be time to re-examine the threshold for EMBx in clinical care.

Conflict of interest statement

Milan Dusík, Anees Daud, Ondřej Šmíd, Štěpán Havránek, Ivana Vítková, Patricia Monica Revelo, Josef Stehlik, Aleš Linhart and Jan Bělohlávek declare that they have no conflict of interest.

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