

The chameleon of cardiology: cardiac sarcoidosis before and after heart transplantation

Farbod Sedaghat-Hamedani^{1,2}, Elham Kayvanpour^{1,2}, Sonja Hamed¹, Lutz Frankenstein¹, Johannes Riffel¹, Weng-Tein Gi^{1,2}, Ali Amr^{1,2}, Omid Shirvani Samani^{1,2}, Jan Haas^{1,2}, Tobias Miersch¹, Esther Herpel^{3,4}, Michael M. Kreuzer^{1,2}, Philipp Ehlermann^{1,2}, Hugo A. Katus^{1,2} and Benjamin Meder^{1,2,5*}

¹Department of Medicine III, University of Heidelberg, Heidelberg, Germany; ²German Centre for Cardiovascular Research (DZHK), DZHK (German Centre for Cardiovascular Research), Heidelberg, Germany; ³Tissue Bank of the National Center for Tumor Diseases (NCT), Heidelberg, Germany; ⁴Institute of Pathology, Heidelberg University Hospital, Heidelberg, Germany; ⁵Department of Genetics, Stanford University, Stanford, CA 94305, USA

Abstract

Cardiac sarcoidosis is a chronic inflammatory disease with a large spectrum of symptoms that can mimic diseases such as dilated, hypertrophic, or arrhythmogenic cardiomyopathies. It can be asymptomatic but can also present with ventricular arrhythmias, conduction disease, and heart failure (HF) or even sudden cardiac death (SCD). We present here the case of a patient transplanted due to end-stage arrhythmogenic right ventricular cardiomyopathy (ARVC), fulfilling the task force criteria. A few years after successful heart transplantation (HTX), the patient developed similar symptoms and morphofunctional changes of the heart, which led to critical re-evaluation of his primary diagnosis.

Keywords Cardiac sarcoidosis; Arrhythmogenic right ventricular cardiomyopathy (ARVC); Heart transplantation

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*Correspondence to: Benjamin Meder, Department of Medicine III, University of Heidelberg, INF 410, Heidelberg 69120, Germany.

Email: benjamin.meder@med.uni-heidelberg.de

Introduction

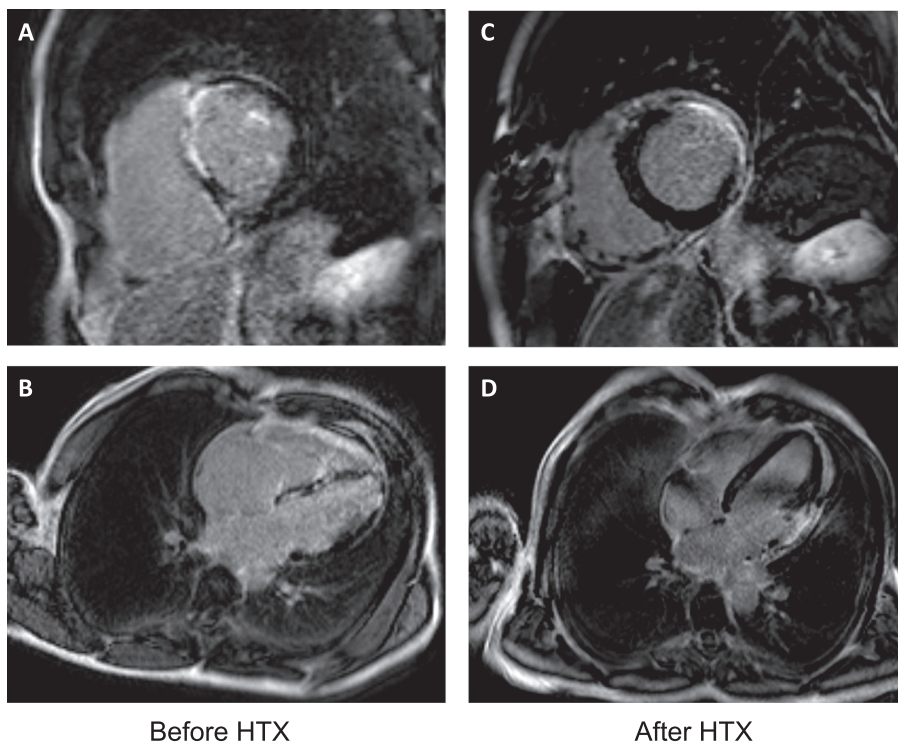
Cardiac sarcoidosis is an inflammatory granulomatous cardiac disease of unknown aetiology. It may be caused by an immunological response to an unidentified antigenic trigger in genetically predisposed individuals.^{1,2} The clinical manifestation of cardiac sarcoidosis depends on the location of granulomatous inflammation ranging from asymptomatic to fatal arrhythmias and severe heart failure, which sometimes requires heart transplantation.³ Therefore, early diagnosis of cardiac sarcoidosis is essential. However, making the diagnosis is a challenge. It can mimic diverse cardiac diseases such as arrhythmogenic right ventricular cardiomyopathy (ARVC), dilated cardiomyopathy (DCM), amyloidosis, myocardial infarction, Chagas disease, or myocarditis.⁴ Here, we report the case of a patient with cardiac sarcoidosis, who was misdiagnosed with ARVC, fulfilling the task force criteria (severe dilatation and reduction of RV in cMRI, inverted T waves in V1 and V2 in the absence of complete right bundle-branch block, fibrous replacement in endomyocardial biopsy, and

sustained ventricular tachycardia in electrophysiology study).⁵ He subsequently underwent heart transplantation (HTX) due to severe heart failure, developed however a few years afterwards similar symptoms and signs as before.

Case report

A 46-year-old male patient presented to our cardiology department with dyspnoea and reduced exercise capacity with no family history for cardiomyopathies, heart failure, or sudden cardiac death. The echocardiography (TTE) showed a mildly reduced left ventricular ejection fraction (LV-EF = 50%) with anteroseptal and inferoapical hypokinesia and a dilated right ventricle. Cardiac magnetic resonance imaging (cMRI) showed transmural late gadolinium enhancement (LGE) in RV and LV with severely reduced RV-EF (Figure 1A–B). The coronary angiography showed no significant coronary stenosis. LV endomyocardial biopsy showed interstitial fibrosis with no signs of acute or borderline myocarditis (negative

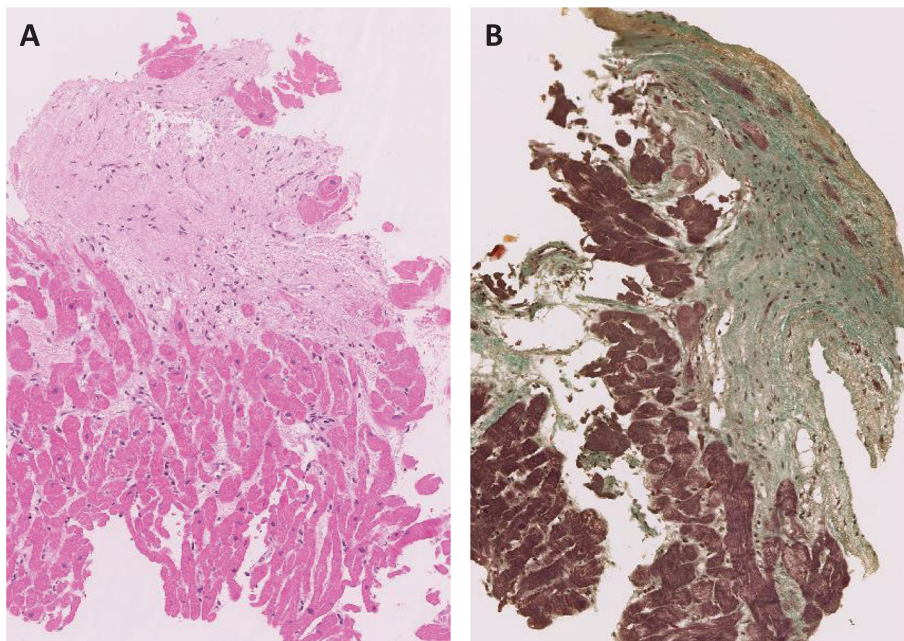
Figure 1 Cardiac magnetic resonance imaging (cMRI) before and after heart transplantation (HTX). cMRI showed similar transmural late gadolinium enhancement (LGE) in RV and LV before and after HTX (A and C short axis view, B and D four chamber view).



Dallas criteria) and no storage disease (*Figure 2*). Due to a suspected ARVC and because of inducible, monomorphic, sustained ventricular tachycardia (VT), the patient received

an implantable cardioverter-defibrillator (ICD). In the course of his treatment (Ramipril, Metoprolol, and Torasemide), the dyspnoea worsened and RV-EF deteriorated, LV-EF was

Figure 2 Left ventricular endomyocardial biopsy. LV biopsy showed interstitial fibrosis with no signs of myocarditis (A, hematoxylin and eosin staining; B, trichrome staining).



26%. Patient's pharmacological HF therapy was optimised based on guidelines for heart failure and he was listed for HTX, which he received 2 years after his first presentation. There were no perioperative complications and immunosuppressive therapy could be reduced as in-house protocols. The initial immunosuppressive medications were Methylprednisolone, Mycophenolate, and Tacrolimus. Methylprednisolone phased out gradually. One year after HTX, the TTE showed a mildly reduced LV function with mid-ventricular hypokinesia. Furthermore, the cMRI showed a dilated RV with mildly reduced RV-EF and transmural LGE in left circumflex artery (LCX) area (Figure 1C–D). Due to the cMRI, a silent myocardial infarction (MI) was suspected, however, the coronary angiography showed no pathological findings. Moreover, endomyocardial biopsies showed no sign of transplant rejection. To exclude paradoxical embolism as cause of MI, after excluding atrial fibrillation, a transoesophageal echocardiography (TEE) was performed. This showed a patent foramen ovale (PFO), which was treated with an Amplatzer closure device. Four years after HTX the patient was admitted to the intensive care unit (ICU) after cardiopulmonary resuscitation (CPR) due to ventricular fibrillation (VF) and received an ICD as secondary prophylaxis. During the following 3 years, the RV function reduced progressively, and the patient developed severe RV dilation and tricuspid regurgitation. The RV stimulation threshold of the ICD increased from 0.4/0.5 to 1.6/0.5 V/ms. Under diuretics and optimisation of pharmacological HF therapy the disease progress could be initially controlled. However, over the following 3 years, dyspnoea worsened (NYHA III), the LV-EF decreased (EF = 40% by TTE) and showed basal inferior and inferolateral hypokinesia. Moreover, the RV-EF reduced severely, and the RV stimulation threshold increased to 2.2/0.5 V/ms. At this time point, clinical records of the patient were critically re-evaluated in the Institute for Cardiomyopathy Heidelberg with regards to

specific aetiologies and a cardiac sarcoidosis as initial cause was suspected. To render ARVC as cause of HTX and disease of the donor unlikely, genetic investigation using panel sequencing was investigated (Figure 3). No pathogenic or likely pathogenic ARVC variants, neither in patient's DNA nor in the DNA from the myocardial biopsy of the transplanted heart could be identified. A positron-emission tomography (PET-CT) with F-18 FDG confirmed active cardiac sarcoidosis (Figure 4) and made this the most probable cause of initial cardiac disease in the patient after 12 years (Figure 5). The immunosuppressive therapy was adjusted consequently. Due to severe, decompensated right ventricular heart failure and severe tricuspid valve regurgitation, the patient underwent an operative valve replacement. However, he died post-operatively due to recurrent hemodynamically relevant sustained ventricular arrhythmia.

Discussion

Sarcoidosis is a systematic inflammatory disease of unknown aetiology and may involve every organ.⁶ Whereas the lungs are involved in 90% of patients, cardiac involvement has been reported to be as low as 5%.^{1,7} Other, postmortem studies could however detect cardiac involvement in up to 25–40% of pulmonary sarcoidosis patients.^{7,8} Isolated cardiac sarcoidosis can also occur, and it is more common than previously suspected.⁴

Whereas each part of the heart can be involved; granulomas have been mostly found in the left ventricular free wall and basal interventricular septum.⁷ Clinical features of cardiac sarcoidosis depend on this locations leading to conduction disease, fatal ventricular arrhythmias, sudden cardiac

Figure 3 Schematic illustration of genetic analysis. No pathogenic or likely pathogenic ARVC variants, neither in patient, nor in the DNA from the myocardial biopsy of the donor heart could be detected.

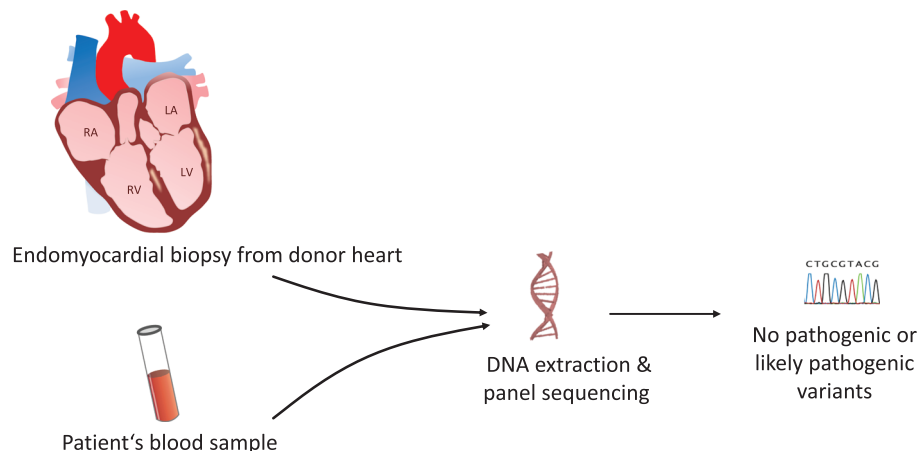
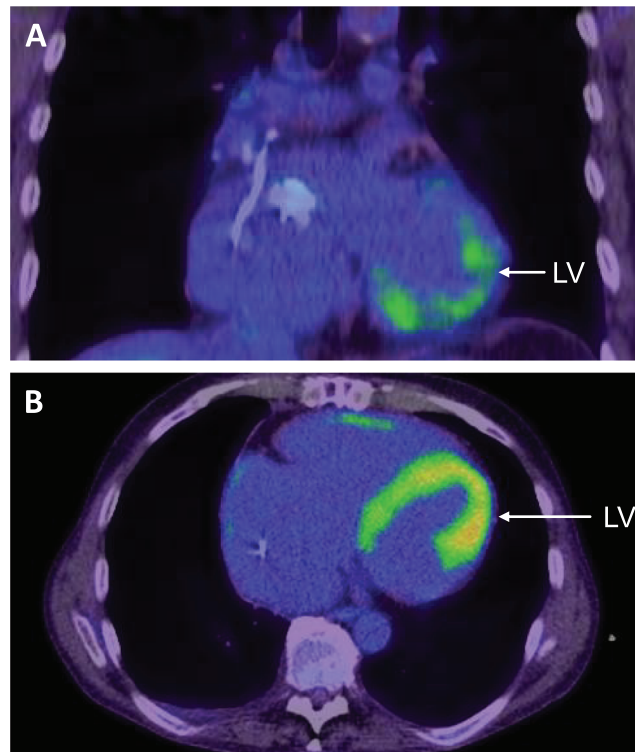


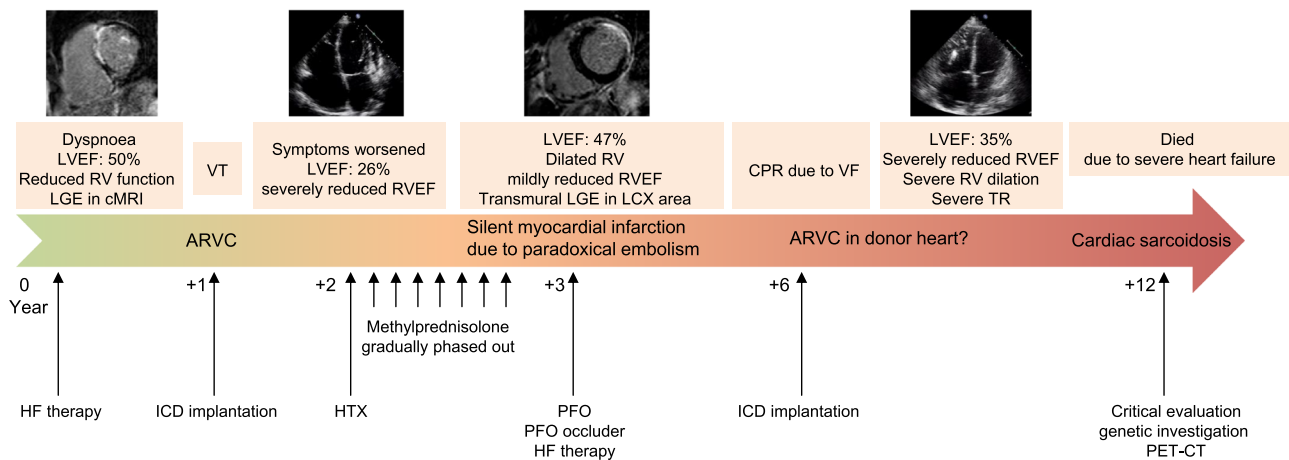
Figure 4 Positron-emission tomography (PET-CT) with F-18 FDG. PET-CT confirmed the active cardiac sarcoidosis. LV, left ventricle.



death, or severe heart failure.^{1,9} This is why it can mimic different cardiac diseases, especially ARVC or silent myocardial infarction as seen in this case report. Given the potential fatal prognosis, early diagnosis and treatment of cardiac sarcoidosis is critical and may be lifesaving.⁴

The definitive diagnosis of isolated cardiac sarcoidosis is a challenging task. Although histopathological findings can confirm the definitive diagnosis, it has a high false negative rate due to sampling error.⁷ Because cardiac involvement is mostly ‘patchy’ and granulomas are often located in the basal

Figure 5 Disease progression timeline. The patient was initially diagnosed with arrhythmogenic right ventricular cardiomyopathy (ARVC) and transplanted due to end-stage heart failure. A few years after heart transplantation (HTX), the patient developed similar symptoms and morpho-functional changes of the heart, which led to diagnosis of cardiac sarcoidosis. cMRI, cardiac magnetic resonance imaging; EF, ejection fraction; HF, heart failure; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LV, left ventricle; PET-CT, positron-emission tomography; PFO, patent foramen ovale; RV: right ventricle; VF, ventricular fibrillation; VT, ventricular tachycardia.



interventricular septum, myocardial biopsies have difficulties reaching them.¹⁰ Currently, gadolinium-enhanced cardiac magnetic resonance imaging (cMRI) and positron emission computed tomography (PET/CT) are the diagnostic modalities with best compromise between specificity and sensitivity for cardiac sarcoidosis.^{3,4,11}

Patients with cardiac sarcoidosis and end-stage heart failure have a poor prognosis without heart transplantation (HTX).¹² After HTX, they have an acceptable long-term outcome.¹³ Zaidi *et al.* observed a 5-year survival rate of 80.5% in 65 heart transplant recipients with cardiac sarcoidosis.¹³ Recurrent cardiac sarcoidosis has been rarely reported.^{12,14,15}

It is reported in 0–14% of patients with cardiac sarcoidosis after heart transplantation.^{12,13,15} In order to rule out recurrence of cardiac sarcoidosis in heart transplanted patients, they should be carefully evaluated, not only via endomyocardial biopsy but also using cMRI. Maintaining patients on low doses of corticosteroids may prevent a recurrence in the cardiac allograft.¹²

Conclusions

Cardiac sarcoidosis is an inflammatory and often aggressive cardiomyopathy with a low prevalence, which is often misdiagnosed. Early diagnosis and early therapy of cardiac sarcoidosis is crucial and lifesaving. In end-stage cases of cardiac sarcoidosis, HTX is the only therapeutic measure. However, the disease can reoccur in the transplanted heart. Cardiologists should be aware of its diverse and unspecific signs and symptoms, which makes it a chameleon of cardiology. Thus, the evaluation of adequate diagnostic methods such as cMRI is necessarily required in patients before and after HTX in order to rule out this life-threatening disease.

Conflict of interest

None declared.

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