

## CARDIAC SARCOIDOSIS AND HEART TRANSPLANTATION: A REPORT OF FOUR CONSECUTIVE PATIENTS

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**ABSTRACT.** Heart transplantation (HTx) is a well-established treatment for severe cardiac failure. However, HTx for cardiac sarcoidosis is rare; less than 80 patients have been reported worldwide. In many patients, the diagnosis was not made prior to HTx. The aim of this study was to describe the use of HTx in the treatment of severe cardiac sarcoidosis. The series was comprised of four Caucasian patients (1 male, 3 females), aged 25-57 years. HTx were performed in the period 1990-2006. None of the patients had clinically overt extra-cardiac sarcoidosis. In one patient the diagnosis of sarcoidosis was proven prior to HTx. In three patients, all with dilated cardiomyopathy due to myocardial sarcoidosis, the final diagnosis was obtained by examination of the explanted heart. Arrhythmias (supraventricular and ventricular), heart block, mitral valve insufficiency and dilated cardiomyopathy were prominent clinical features. None of the patients had recurrence of sarcoid disease in the allograft. Two patients are long-term survivors and two are deceased, one of primary graft failure, the other from Cytomegalovirus myocarditis. In conclusion, HTx is a viable treatment for cardiac sarcoidosis with end stage cardiac failure. Cardiac sarcoidosis is difficult to diagnose. Myocardial biopsy has a low diagnostic sensitivity. However, when the newest non-invasive diagnostic methods, including magnetic resonance imaging and positron emission tomography, are applied, an endomyocardial biopsy should not be mandatory to make a diagnosis of cardiac sarcoidosis. (*Sarcoidosis Vasc Diffuse Lung Dis* 2008; 25: 51-59)

**KEY WORDS:** dilated cardiomyopathy, heart block, heart transplantation, sarcoidosis, ventricular tachycardia

### INTRODUCTION

Heart transplantation (HTx) is the definitive treatment in patients with severe heart failure secondary to sarcoid cardiomyopathy (1). Since the first HTx in 1967, more than 80,000 transplantations have

been performed worldwide (2). However, there has been reluctance to perform HTx in sarcoidosis given concerns about recurrence of the disease in the allograft (1). In the USA, sarcoidosis constitutes an indication for HTx in less than 0.2% of the patients (1). The exact number of patients who have undergone HTx due to cardiac sarcoidosis has not been reported (2), but probably less than 100 patients have been transplanted worldwide; nine of these patients have been reported in detail (3, 4, 5, 6, 7, 8, 9). In the period 1990-2006, our centre performed 250 HTx, including four (1.6%) patients with cardiac sarcoidosis.

The diagnosis of sarcoid heart disease remains a challenge to the clinician, and in four of the nine reported cases, the diagnosis had apparently not been

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made prior to HTx (4, 7, 9). In this paper we describe four Caucasian patients having HTx due to sarcoid cardiomyopathy. In three patients the true nature of the disease was first disclosed by examination of the explanted recipient heart.

## CASES

### Case 1

A 25-year-old woman without diabetes mellitus, arterial hypertension, hypercholesterolaemia, cardiovascular disease or sarcoidosis. No alcohol abuse. She was healthy until the age of 25 years when she developed heart failure due to dilated cardiomyopathy during her first pregnancy. Electrocardiography (ECG) showed intermittent non-sustained ventricular tachycardia. A Caesarean section was performed. Apart from signs of heart failure, the clinical examination, chest X-ray and pulmonary function were normal and there were no manifestations of extra-thoracic sarcoidosis. Myocardial biopsy was not performed. A diagnosis of postpartum cardiomyopathy was made. Subsequently, the patient had repeated episodes of cardiac arrest elicited by ventricular tachycardia and ventricular fibrillation. Over a few months her condition deteriorated and the patient became New York Heart Association (NYHA) functional class IV. Right-sided cardiac catheterization showed a cardiac output of 3.4 L/min. Glomerular filtration rate was 74 ml (min x 1.73 m<sup>2</sup>). She remained hospitalized for one year until HTx was performed in October 1990 (the first HTx in Denmark). The perioperative course was uncomplicated. Prophylaxis against *Cytomegalovirus* (CMV) and *Pneumocystis carinii* was not available at the time of HTx, but there were no post-transplant infectious episodes.

Macroscopic examination of the explanted recipient heart showed a normally formed heart measuring 12.5 x 13 x 9.9 cm without atria (supra-avalvular explantation). The epicardium had a slight degree of fibrosis with a moderate amount of adipose tissue.

Right midventricular cross-sectional diameter measured 2.3 cm, left ventricular cross-sectional diameter was 6.6 cm. Thickness of ventricular walls: right free 3 mm, septum 11 mm, left anterior 8 mm, left lateral 7 mm and left posterior 10 mm. There

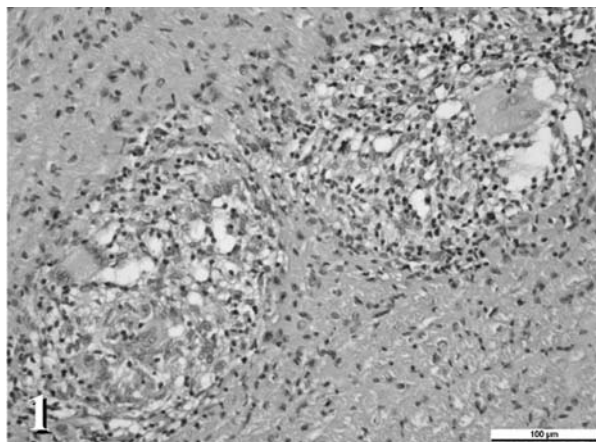
was slight disperse fibrosis in the myocardium. There were endocardial changes consistent with ventricular dilation.

The endocardium in the left ventricle showed focal sclerotic thickening. Microscopic examination demonstrated scattered and, in many areas, ill-defined epithelioid cell granulomas without necrosis dispersed in the myocardium, often associated with a slight degree of fibrosis. The granulomas were predominantly located in the deeper parts of the myocardium and included a small rim of lymphocytes (Fig. 1). There was no involvement of the pericardium or epicardium. The cardiomyocytes were hypertrophic.

Two years after HTx, cardiac catheterization showed normal haemodynamics with left ventricular ejection fraction (LVEF) 67%, aortic pressure 133/85 mm Hg, pulmonary artery pressure 24/14 mm Hg (mean 16 mm Hg), cardiac output 5.7 L/min and cardiac index 2.9 L/min/m<sup>2</sup>.

Post-transplant transvenous right ventricular endomyocardial surveillance biopsies have been performed twenty three times, the last 10.3 years after HTx. There have been four episodes of mild focal acute rejection (grade IA) according to the classification system of the International Society of Heart and Lung Transplantation. None of the biopsy specimens has shown recurrence of sarcoidosis in the cardiac allograft.

Coronary angiography ten years after HTx was normal. Repeat angiography fifteen years after HTx



**Fig. 1.** Biopsy from the explanted recipient heart in Case 1. Sarcoid granulomas in the myocardium with epithelioid cells and multinucleated giant cells surrounded by T-lymphocytes (haematoxylin-eosin staining).

showed atherosclerosis and occlusion of the left anterior descending coronary artery. There were no symptoms of cardiovascular disease. Glomerular filtration rate has stabilized at 44 ml (min x 1.73 m<sup>2</sup>). At follow-up fifteen years after HTx the patient is doing well and is in NYHA Class II. There have been no signs of extracardiac sarcoidosis.

### *Case 2*

A 46-year-old woman without diabetes mellitus, arterial hypertension, hypercholesterolaemia, cardiovascular disease or sarcoidosis. She was healthy until the age of 43 years when she developed exertional dyspnea and intermittent irregular heart rhythm. Echocardiography disclosed dilated cardiomyopathy with an LVEF of 25% and secondary mitral valve insufficiency. ECG showed intermittent ventricular tachycardia, complete heart block and left bundle branch block. A VVI pacemaker was implanted and the patient began anti-arrhythmic treatment with amiodarone. Transvenous right ventricular endomyocardial biopsy (three biopsy specimens) revealed epithelioid cell granulomas and the patient was started on prednisolone. A repeat endomyocardial biopsy two months later showed no granulomas and prednisolone was discontinued. There were no clinical signs of extracardiac sarcoidosis and computed tomography (CT) of the thorax was normal. In February 1991, due to dilated cardiomyopathy with progressive heart failure (NYHA Class IV), HTx was performed.

By macroscopic examination, the explanted heart measured 11 x 12.5 x 7.5 cm. Cross-sectional diameter of the right ventricle was 3.3 cm and the left ventricle 6.5 cm. The right ventricular free wall had a varying thickness of 1 to 5 mm; thickness of the left midventricular lateral wall was 10 mm, left anterior wall 9 mm, left posterior wall 11 mm and septum 13 mm. There was diffuse fibrosis throughout the myocardium. The right ventricular wall showed partial thinning with inconspicuous muscle tissue. Both ventricular chambers showed significant endocardial fibrosis. The cardiac valves were normal. The epicardium showed focal fibrosis. Microscopic examination revealed multiple widespread transmural epithelioid cell granulomas with multinucleated giant cells but without necrosis. The granulomatous inflammation was intensified in the central parts of the myocardium and severely affected the conductive

tissue close to the annulus fibrosus. In the right ventricle, a major part of the free wall was transformed into homogenous connective tissue and there was diffuse fibrosis in the remaining part of the heart. There was a mild chronic nonspecific pericarditis. The coronary arteries were normal.

The patient died two months after transplantation due to ventricular fibrillation, possibly induced by CMV myocarditis and CMV pneumonitis. Autopsy showed no recurrence of sarcoidosis in the cardiac allograft. The mediastinal lymph nodes, lungs and spleen contained epithelioid cell granulomas, which substantiated the diagnosis of sarcoidosis.

### *Case 3*

A 35-year-old woman without diabetes mellitus, arterial hypertension, hypercholesterolaemia, cardiovascular disease or sarcoidosis. She had a smoking history of 20 pack-years and was still smoking 5 cigarettes/day at referral. There was no alcohol abuse. She was healthy until the age of 32 years when she developed slight exertional dyspnea and irregular heart rhythm. At the age of 34 years she had progressive exertional dyspnea. Coronary angiography was normal. ECG showed intermittent atrial fibrillation. Echocardiography disclosed dilated cardiomyopathy. High resolution CT (HRCT) of the thorax showed pulmonary congestion and slightly enlarged lymph nodes on the right side of the trachea and along the aortic arch. The lung parenchyma was normal. Biopsy of the mediastinal lymph nodes was not performed. There were no clinical manifestations of extra-thoracic sarcoidosis.

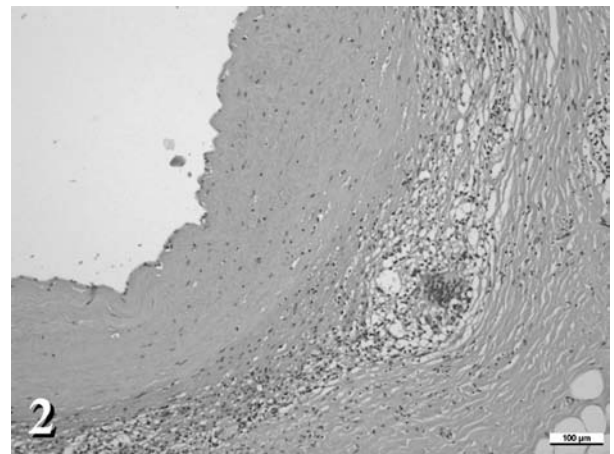
Over a few months, her condition deteriorated and at referral she was classified as NYHA Class IV. Physical examination disclosed an arterial blood pressure of 97/59 mm Hg. There was no jugular venous distension or peripheral edema. The liver could be palpated 6 cm below the curvature. ECG showed sinus tachycardia at 116 beats/min with a normal PR interval (0.14 ms), normal QRS duration (80 ms) but incomplete right bundle branch block and low voltage. Echocardiography disclosed moderate to severe dilation of the left ventricle (left ventricular end-diastolic diameter = 67 mm) and global thinning of the left ventricular wall, with a LVEF of 15-20%. There was secondary mitral valve insufficiency grade 2 and tricuspid valve insufficiency grade 2. Initially, right-sided

cardiac catheterization showed: cardiac output 3.4 L/min, cardiac index 1.9 L/min/m<sup>2</sup>, pulmonary artery pressure 73/32 mmHg (mean 48 mm Hg), and mean pulmonary wedge pressure 38 mm Hg. Right ventricular pressure was 72/10 mm Hg (mean 14 mm Hg), left ventricular end diastolic pressure 30 mm Hg and pulmonary vascular resistance 2.9 Wood Units. Following medical treatment for heart failure, the values improved slightly: cardiac output 3.0 L/min, cardiac index 1.7 L/min/m<sup>2</sup>, pulmonary artery pressure 42/22 mmHg (mean 29 mm Hg), and mean pulmonary wedge pressure 25 mm Hg. Right ventricular pressure was 42/7 mm Hg (mean 6 mm Hg) and femoral artery pressure 88/51 mm Hg. Pulmonary vascular resistance had fallen to 1.3 Wood Units. Pulmonary hypertension was considered to be secondary to left ventricular failure and insufficiency of the mitral and tricuspid valves was considered secondary to ventricular dilation. Transvenous right ventricular endomyocardial biopsy from the lower third of the interventricular septum (three large specimens) showed slight myocardial hypertrophy. There was no inflammation, vasculitis, granulomas or giant cells. Pulmonary function tests showed decreased lung function with a restrictive pattern. Forced expiratory volume in the first second (FEV<sub>1</sub>) was 61% of predicted value and forced expiratory vital capacity (FVC) was 62% of predicted. FEV<sub>1</sub>/FVC was 0.88, i.e. increased to 108% of predicted. Diffusion capacity for carbon monoxide (D<sub>L</sub>-CO) was 53% of predicted and D<sub>L</sub>CO/alveolar volume (VA) was 71% of predicted. Arterial blood gases at room air showed hyperventilation with pH 7.6, PaO<sub>2</sub> 6.9 kPa, PaCO<sub>2</sub> 2.7 kPa and saturation (SaO<sub>2</sub>) of 90 %. The decrease in lung function was considered secondary to severe heart failure. Glomerular filtration rate was normal, 84 ml (min x 1.73 m<sup>2</sup>). In May 2003, at the age of 35 years, she underwent HTx. The perioperative course was uneventful.

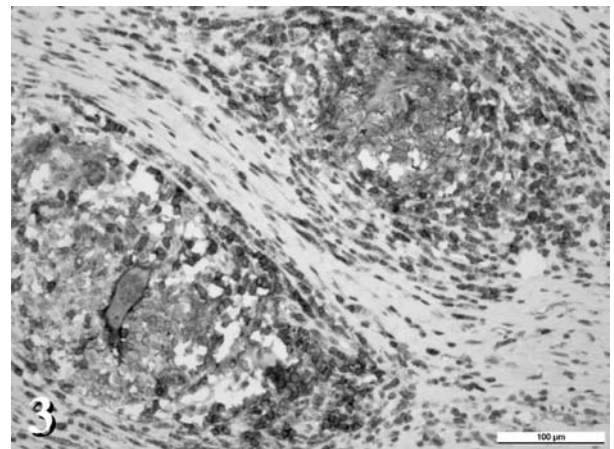
Macroscopic examination of the explanted recipient heart showed a weight of 386 g and extensive focal scarring of the right ventricular wall, the cephalic portion of the interventricular septum and in particular the lateral, anterior and posterior left ventricular walls. Both ventricles were slightly dilated with free wall measurements as follows: right 2-5 mm, left 5-15 mm. The heart valves appeared normal. All epicardial coronary arteries were patent with minor non-occlusive atheromatous plaques. Microscopy disclosed numerous non-necrotizing epithelioid cell granulomas

with multinucleated giant cells and lymphocytes distributed within the endo-, myo- and peri-cardium mainly within the fibrotic areas. Granulomas were also numerous in association with intramyocardial and especially epicardial coronary arteries (Fig. 2), including some of the major branches. The lymphocytes in the granulomas were predominately CD4 positive cells (Figs. 3, 4) and demonstrated along with the macrophages (Fig. 5) strong HLA-DR expression demonstrated by immunohistochemistry.

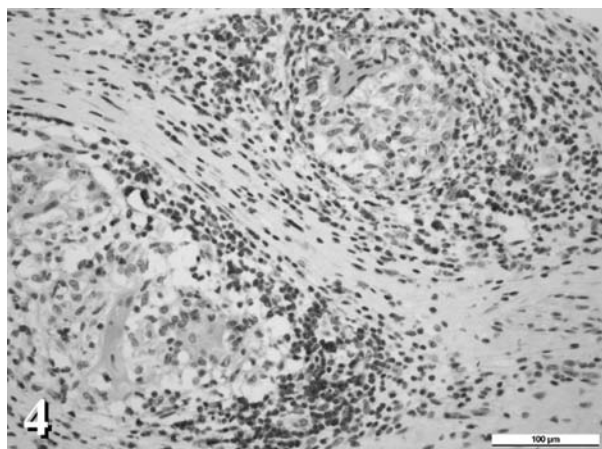
Prophylaxis against CMV and *Herpes simplex virus* infection consisted of gancyclovir for three



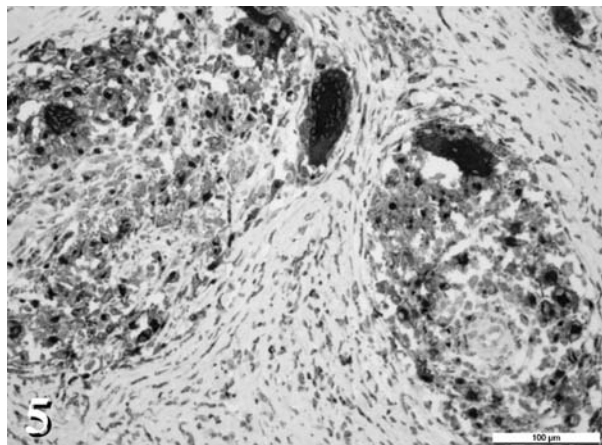
**Fig. 2.** Biopsy from the explanted recipient heart in Case 3. Transmural section of a coronary epicardial artery showing sarcoïd granulomas in the adventitia (haematoxylin-eosin staining).



**Fig. 3.** Immunohistochemical staining for CD4+ T-lymphocytes. Densely stained CD4+ T-lymphocytes are far more numerous than CD8+T-lymphocytes and predominantly located in the periphery of the sarcoïd granulomas. Epithelioid cells in the central part of the granulomas are slightly stained.



**Fig. 4.** Immunohistochemical staining for CD8+ T-lymphocytes located in the periphery of the sarcoid granulomas.



**Fig. 5.** Immunohistochemical staining for CD68+ macrophages showing staining of the epithelioid cells and densely stained multinucleated giant cells.

months after HTx. Prophylaxis against infection with *Pneumocystis carinii*, *Toxoplasma gondii* and *Listeria monocytogenes* consisted of life-long treatment with sulfamethoxazol/trimethoprim. The echocardiogram remains normal, apart from a small pericardial exudate of no haemodynamic significance. Physical performance level is normal. Pulmonary function tests 110 days after HTx showed an improvement in FEV<sub>1</sub> to 75% of predicted and FVC to 75% of predicted. FEV<sub>1</sub>/FVC was 0.78, i.e. it had decreased to normal level (96% of predicted). D<sub>L</sub>CO had decreased to 45% of predicted and D<sub>L</sub>CO/VA had decreased to 57% of predicted value. In September 2003, HRCT of the thorax was unchanged with slightly enlarged mediastinal lymph nodes, normal lung parenchyma and pleura.

Post-transplant surveillance transvenous right ventricular endomyocardial biopsy has been performed nineteen times, the last 2.1 years after HTx. There have been four episodes of mild focal acute rejection (grade IA). None of the biopsy specimens has shown recurrence of sarcoidosis.

#### Case 4

A 57-year-old man, never-smoker, without diabetes mellitus, arterial hypertension, hypercholesterolemia, cardiovascular disease or sarcoidosis. At the age of 56 years, he developed progressive dyspnea on exertion. Echocardiography showed right ventricular dilation with normal function of the left ventricle. Pulmonary ventilation/perfusion scintigraphy showed no evidence of pulmonary embolism.

Shortly after, the patient suffered a cardiac arrest due to ventricular fibrillation and was resuscitated without ensuing cerebral damage. Transvenous endomyocardial biopsy from the right ventricle displayed severe myocardial fibrosis. The patient was initially diagnosed with arrhythmogenic right ventricular dysplasia and a cardioverter defibrillator (ICD) with biventricular pacing was implanted.

Subsequent ECG showed pace rhythm. The patient's condition continued to deteriorate into NYHA class III. A repeat echocardiography showed progressive dilation of the right ventricle with diffuse hypokinesia and a non-dilated, hypertrophic, hypokinetic left ventricle with an LVEF of 25%. Coronary angiography was normal. A repeat endomyocardial biopsy four months later disclosed widespread epithelioid cell granulomas with multinucleated giant cells and without necrosis, compatible with a diagnosis of sarcoidosis.

Clinical and laboratory examination showed no evidence of extra-cardiac sarcoidosis. Lung function and HRCT of the thorax were normal.

Treatment with prednisolone 25 mg/day and azathioprine 150 mg/day was initiated as well as medical treatment for cardiac arrhythmia and heart failure. Whole body F<sup>18</sup>-deoxyglucose-positron emission tomography (FDG-PET) showed no extra-cardiac uptake. However, FDG-PET of the heart showed irregular uptake in the myocardium, consistent with the presence of sarcoid granulomas and fibrosis. Right-sided heart catheterization showed a normal pulmonary artery pressure of 20/8

mmHg (mean 12 mm Hg) and a normal pulmonary vascular resistance of 1 Wood Unit. The patient underwent HTx in January 2006. Regrettably, the explanted heart was not available for examination. The patient died of primary graft failure two days after HTx. At autopsy there was extensive atherosclerosis of the coronary arteries in the implanted heart. There were multiple inactive hyalinized granulomas and fibrosis in the mediastinal lymph nodes, consistent with previously active sarcoidosis.

## DISCUSSION

Sarcoidosis may affect any organ system, although the lungs are the most commonly affected organs (10).

Histology shows epithelioid cell granulomas without necrosis containing multinucleated giant cells and CD4+ T lymphocytes (10). Development of clinical sarcoidosis is associated with exposure to putative infectious antigen(s) together with a genetic predisposition (10). There is a strong racial influence on the disease (10) with sarcoidosis being more prevalent and having a more severe course in African-Americans than in Caucasians (10). This is most likely the case for cardiac sarcoidosis as well. In the USA, 0.41% (19/4686) of black HTx patients had cardiac sarcoidosis versus 0.15% (44/30246) of white HTx patients (1).

Cardiac sarcoidosis was initially described in 1929 (11) and the first death related to the disease was reported in 1937 (12). Due to the low frequency of the disease, the difficulty in making the diagnosis and the lack of large systematic studies, an estimate of the incidence and prevalence of cardiac sarcoidosis remains uncertain.

An autopsy study of eighty-four unselected patients with systemic sarcoidosis showed cardiac involvement (granulomas) in 27% (13) of whom the majority had no cardiac symptoms. Among seven hundred and two European patients with chronic systemic sarcoidosis, 5% had cardiac involvement (14). The incidence of sarcoidosis in Denmark is 7.2 per  $10^5$  person years. The population is  $5.5 \times 10^6$ , i.e. each year approximately 400 new cases of sarcoidosis are diagnosed (15), which would imply approximately 20 new cases of cardiac sarcoidosis. However, the known number of cases with cardiac sarcoidosis in Denmark

is far lower, thus suggesting that the disease is underdiagnosed (16).

A total of seventy-eight cases of HTx for cardiac sarcoidosis have been reported, including the patients in the current study (1, 3, 4, 5, 6, 7, 8, 9). Most cases of cardiac sarcoidosis occur in patients with known systemic sarcoidosis, e.g. pulmonary sarcoidosis. However, cases of apparently isolated cardiac sarcoidosis have been reported (7, 17), which may be a reflection of subclinical disease in extra-cardiac organs.

The patients in cases 1 and 4 of this study had no signs of extra-cardiac sarcoidosis prior to HTx, whereas cases 2 and 3 had slightly enlarged mediastinal lymph nodes. At autopsy, sarcoid lesions were present in mediastinal lymph nodes in cases 2 and 4; no biopsy was performed in case 3.

Cardiac sarcoidosis has a broad clinical spectrum and can mimic heart diseases of many other aetiologies including ischaemic heart disease. The most common clinical manifestations are conduction disturbances (cases 2, 3), ventricular arrhythmias (cases 1, 2, 4), supraventricular arrhythmias (case 3), heart valve insufficiency (cases 2, 3) and congestive heart failure (cases 1, 2, 3, 4) often mimicking idiopathic dilated cardiomyopathy (18, 19). Cases 1, 2 and 3 presented with dilated cardiomyopathy, which was considered to be idiopathic, whereas case 4 had an initial diagnosis of arrhythmogenic right ventricular dysplasia. It is difficult to discriminate idiopathic dilated cardiomyopathy from cardiac sarcoidosis although the latter has a higher frequency of complete heart block, right bundle branch block and abnormal left ventricular wall thickness (20).

Complete heart block occurs in approximately 30% of patients with cardiac sarcoidosis and among these, 68% have syncope (21). Right bundle branch block is reported in approximately 57% of patients with cardiac sarcoidosis and is more frequent than left bundle branch block (20). Typically patients with cardiac sarcoidosis develop complete heart block at a younger age than those with idiopathic heart block. Complete heart block in a young patient may therefore be a clue to the diagnosis of cardiac sarcoidosis. The majority of patients with heart block have granulomas or fibrosis in the basal interventricular septum at autopsy (cases 2, 3) (22).

Supraventricular arrhythmias occur with an incidence of approximately 19% (21). Sarcoid granulomas in the atria may act as foci for ectopic tachycardia, atrial flutter or atrial fibrillation. Sinus arrest can be a

consequence of granulomas in the sinus node (23). Ventricular tachycardia (both non-sustained and sustained) and ventricular ectopy is reported in 23% of patients (cases 1, 2, 4) (21). Ventricular tachycardia or ventricular fibrillation is probably the most frequent cause of sudden death in cardiac sarcoidosis as observed in the patient in case 4 who had a cardiac arrest due to ventricular fibrillation.

The most frequent valvular dysfunction in cardiac sarcoidosis is mitral valve insufficiency (case 2, 3) (19). Seldom, insufficiency of the aortic, tricuspid (case 3) and pulmonary valves has been reported.

Heart failure is the second most frequent cause of death in cardiac sarcoidosis. Granulomatous infiltration in the myocardium may induce decreased systolic function and/or diastolic dysfunction due to increased wall stiffness (24, 25). Patients with heart failure may present with clinical features of both restrictive and/or dilated cardiomyopathy. In a Danish series of forty-four consecutive patients with dilated cardiomyopathy, examined by echocardiography and transvenous endomyocardial biopsy, cardiac sarcoidosis was found in one patient, i.e. 2.3% (26). In a UK series of 453 patients (age 15-81 years) who had an unexpected, sudden, non-ischaemic cardiac death, granulomatous myocarditis was found in 2.2% (27). Cardiac sarcoidosis presents a diagnostic challenge to the clinician. The diagnostic approach in patients with extracardiac sarcoidosis should, as a minimum, include a thorough history of cardiac symptoms, ECG, Holter monitoring and echocardiography (19). Depending on the results of these studies, further investigation with magnetic resonance imaging (MRI) and PET should be performed. In a Danish series of patients with pulmonary sarcoidosis ( $n = 244$ ), ECG abnormalities at rest were found in 14%, of whom 49% had heart block, bundle branch block or ventricular ectopy (28). In a Swedish study of patients with pulmonary sarcoidosis ( $n = 149$ ), ECG abnormalities at rest were found in 21%, of whom 65% had heart block, bundle branch block or atrial fibrillation (29). Holter monitoring for 24 hours or longer may reveal arrhythmias that are missed by routine ECG (30). Echocardiography is a non-invasive, low-cost procedure, which may identify changes caused by sarcoidosis and furthermore yield prognostic information (19). Granulomatous infiltration in the myocardium can be recognized as ventricular wall thickening, especially in the inter-ventricular septum. At later stages, scarring with fi-

brosis is recognized as thinning of the myocardium and aneurysms may be noted.

MRI has been used to an increasing extent to diagnose cardiac sarcoidosis and to evaluate the response to immunosuppressive treatment (9). Both the pericardium and myocardium can be visualized (31). Contrast enhanced (gadolinium diethyl triamin penta-acetic acid) MRI is a promising diagnostic tool in the evaluation of cardiac sarcoidosis, although the sensitivity and specificity remain to be determined. Regional enhancement can represent aggregates of sarcoid granulomas, whereas a reduced signal is seen with fibrotic scarring.

Sarcoid granulomas are active metabolic structures, which have a high uptake of glucose and consequently of  $F^{18}$ -fluorodeoxyglucose (FDG).

FDG-PET appears to be a sensitive non-invasive method to evaluate inflammatory activity in the granulomas (32, 33) both from a diagnostic and therapeutic point of view, although the sensitivity and specificity require further clarification.

Endomyocardial biopsy is usually performed by the transvenous approach from the peripheral septal portion of the right ventricle. It is an invasive procedure with risk of complications (34), but represents the gold standard to ensure a solid diagnosis of cardiac sarcoidosis.

Unfortunately, the diagnostic sensitivity is low due to the patchy involvement of the myocardium and the higher incidence of granulomas in the basal ventricular septum and the left ventricle. In patients with histologically verified extracardiac sarcoidosis who have clinical signs of cardiac sarcoidosis, endomyocardial biopsy reveals granulomas in only 20-50%, which implies that a negative biopsy does not exclude cardiac sarcoidosis (35, 36). When the newest non-invasive diagnostic methods, including MRI and PET, are applied, an endomyocardial biopsy does not seem to be mandatory in making a diagnosis of cardiac sarcoidosis.

The medical treatment of cardiac sarcoidosis consists of immunosuppression with prednisolone combined with azathioprine or methotrexate (8, 37).

Although controlled studies are pending, a number of publications have reported a beneficial effect of this regimen (19). Tumour necrosis factor alpha (TNF- $\alpha$ ) is a key cytokine in the formation of sarcoid granulomas (37, 38). The role of TNF- $\alpha$  inhibitors in the treatment of cardiac sarcoidosis is not clear and should be evaluated in controlled studies.

Patients with arrhythmias should receive standard anti-arrhythmic treatment and the management of heart failure is similar to that in heart failure from other causes (19). Pacemaker or implantable cardioverter-defibrillator should be used in patients with heart block and/or ventricular arrhythmias (case 2) (19) as these procedures reduce the risk of sudden death.

HTx is considered to be the definitive treatment in patients with cardiac failure due to isolated cardiac sarcoidosis who are in NYHA class III-IV (1).

HTx improves the prognosis and quality of life (1, 2). The overall risk of acute cellular rejection within the first year post-transplant is similar in sarcoid patients and patients with other diagnoses (43 vs. 51%) (1). The overall risk of operative death after HTx (one month mortality) in our centre is 5.9% (39), which is lower than the approximate 25% risk (1 of 4) in the patients presented in the current study. In the USA series, the risk of operative death was 6.2% (4 of 65) (1). The overall one and five year survival rates after HTx in our centre are 89% and 79%, respectively (39) vs. 50% in the four patients described.

In the USA series, the one-year post-transplant survival was significantly better for sarcoid patients as compared with contemporaneous patients receiving transplantation for all other diagnoses (87.7 vs.

84.5%) and the long-term 5-year survival was 80.5%, i.e. similar to that in non-sarcoid heart disease (1, 39). HTx patients undergo life-long follow-up, which is most intensive in the first year after transplantation.

Our follow-up protocol is similar in patients with sarcoidosis and patients with other heart diseases. According to our protocol, the immunosuppressive regimen after HTx consists of induction treatment with anti-thymocyte globulin (ATG) and maintenance treatment with cyclosporine, azathioprine or mycophenolate mofetil and prednisolone 5 mg/day. Moderate to severe rejection episodes are treated with intravenous methylprednisolone 1 g/day for three days followed by high doses of prednisolone, which subsequently are tapered to maintenance dose. Prophylaxis against CMV infection consists of valgancyclovir for three months after HTx and against *Pneumocystis carinii* infection of life-long sulfamethoxazol/trimethoprim. During the first post-transplant year at least 14 scheduled surveillance endomyocardial biopsies, ECG's and echocardiographies are performed as well as approximately 20 clinical controls

and regular blood sampling to monitor immunosuppressive therapy. In patients undergoing lung transplantation for pulmonary sarcoidosis, approximately 50% of the patients develop recurrence of sarcoidosis in the lung allograft, which does not influence outcome in the short term (40).

Most patients with sarcoidosis are not considered candidates for HTx because of concerns about recurrence in the cardiac allograft (1). Recurrence of sarcoidosis in the cardiac allograft can occur within 24 weeks (6) to 19 months (8) post HTx. Three of the reported 13 patients, i.e. 23%, having HTx for cardiac sarcoidosis, developed recurrence in the cardiac allograft (6, 8, 9). In this series, none of our two long-term survivors had recurrence. Possible transmission of sarcoidosis from donor to recipient in HTx has also been reported (41, 42). Sarcoid recurrence episodes should be suspected when there are signs of increasing extrathoracic sarcoid activity (9), when the patient develops clinical/laboratory signs compatible with cardiac sarcoidosis (see above) or when endomyocardial biopsies show granulomas (6, 8). Cardiac MRI (9, 31) and to some extent PET (33) may help in establishing the diagnosis. Sarcoid recurrence responds favourably to increased doses of corticosteroids (6, 8, 9). Therefore, in our opinion, and in accordance with the opinion of other authors (1) the risk of recurrence should not be considered a contraindication for HTx.

Heart-lung transplantation (HLTx) might be indicated in concomitant end-stage sarcoid lung disease and sarcoid cardiomyopathy. However, to our knowledge, there is no report on HLTx in sarcoidosis. This may be due to the scarcity of these specific patients or the priority given in consideration of the shortage of donor organs.

In conclusion, cardiac sarcoidosis is a great imitator, which is difficult to diagnose. However, in younger patients, the diagnosis should always be borne in mind especially in subjects with heart block or ventricular arrhythmias. A diagnosis of sarcoidosis should not disqualify candidates for cardiac transplantation.

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