

HEART TRANSPLANTATION FOR ADVANCED HEART FAILURE DUE TO CARDIAC SARCOIDOSIS

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ABSTRACT. *Background:* Selected patients with cardiac sarcoidosis undergo heart transplantation, but outcomes may be adversely affected by recurrent cardiac sarcoidosis or progressive extra-cardiac sarcoidosis. *Objectives:* We present our single-center experience of patients with cardiac sarcoidosis who underwent heart transplantation. *Methods:* Consecutive patients that underwent heart transplantation between 1990 and 2012 were assessed. Cardiac sarcoidosis was defined by the presence of multiple non-caseating epithelioid cell granulomata in the explanted heart. Baseline characteristics and clinical outcomes were compared with a control group without cardiac sarcoidosis that underwent heart transplantation during this period. *Results:* 901 patients underwent heart transplantation during the study period, of whom 4 patients had a pre-transplant diagnosis of cardiac sarcoidosis and 8 patients had sarcoidosis identified in the explanted heart. Patients with cardiac sarcoidosis had excellent post-transplant outcomes with survival of 92% at one year and 83% at five years. Survival was similar to patients that underwent heart transplantation for an alternate diagnosis. We did not encounter recurrent cardiac sarcoidosis or progressive extra-cardiac sarcoidosis during 1001 months of follow-up. *Conclusions:* Carefully selected patients with advanced heart failure due to cardiac sarcoidosis have an acceptable outcome after transplantation. Cardiologists should be aware that reported experience of transplantation for cardiac sarcoidosis mostly represents isolated cardiac sarcoidosis that was only diagnosed at pathological examination of the explanted heart. (*Sarcoidosis Vasc Diffuse Lung Dis* 2015; 32: 208-214)

KEY WORDS: sarcoidosis, cardiac sarcoidosis, heart transplantation

INTRODUCTION

Sarcoidosis is a non-caseating, granulomatous multi-system disorder of unknown etiology. Most

patients present with pulmonary involvement. Other commonly affected organs are lymph nodes, skin, eye, central nervous system and gastrointestinal system but theoretically any organ can be involved. The heart may be the only affected organ or may precede, follow, or occur concurrently with other organ involvement and is associated with a poor prognosis (1). Cardiac involvement appears to be uncommon, affecting only 2-5% of patients with sarcoidosis (2,3). However, autopsy studies show evidence of cardiac involvement in 20-25% of patients dying of sarcoidosis (4,5). This may reflect difficulties in diagnosis; repeated or imaging-guided en-

Received: 25 August 2014?

Accepted after revision: 12 February 2015

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domyocardial biopsy or mediastinal lymph node biopsy may be needed to obtain a histological diagnosis (6). Only 40–50% of patients with cardiac sarcoidosis diagnosed at autopsy have the diagnosis made during their lifetime (1).

Clinical manifestations of cardiac sarcoidosis are heterogeneous, ranging from asymptomatic status to sudden cardiac death (7). Affected patients may present with high-degree AV block, atrial arrhythmias, malignant ventricular arrhythmia or heart failure. Heart transplantation is an established treatment for patients with cardiac sarcoidosis and advanced heart failure and/or frequent ventricular tachycardia (8–11). However, only small numbers of patients with cardiac sarcoidosis undergo cardiac transplantation, partly because of the rarity of the disease and partly because transplantation is contraindicated where there is extensive extra-cardiac involvement. Moreover, there is concern about post-transplant prognosis because cases of recurrent sarcoidosis in the transplanted heart have been reported (12–14). We present our single-center experience of 12 patients who underwent heart transplantation for advanced heart failure due to cardiac sarcoidosis.

METHODS

Study design

Consecutive patients that underwent heart transplantation at Papworth Hospital between January 1990 and December 2012 were included. Cases of cardiac sarcoidosis were identified through hospital pathological records and defined by the presence of multiple non-caseating epithelioid cell granulomata in the explanted heart. The control group comprised all patients who underwent heart transplantation during the same period, but had no evidence of cardiac sarcoidosis in the explanted heart. Pre-transplant baseline characteristics were recorded for each patient; age, gender, height, weight, serum creatinine, transpulmonary pressure gradient and presence of extra-cardiac sarcoidosis. Transplant listing status (routine or urgent) and allograft ischaemic time were recorded. The following outcomes measures were recorded; death, repeat transplantation, acute rejection, atrial or ventricular arrhythmias, high-grade atrioventricular block, allograft sarcoidosis, progres-

sive extra-cardiac sarcoidosis, end-stage renal failure, malignancy, cardiac allograft vasculopathy (CAV) and renal function. Outcome measures were censored on 1st June 2014.

Statistical analysis

Baseline characteristics are reported as means with standard deviations for continuous variables and by frequencies and percents for categorical variables. The data were assessed for normality using the Shapiro–Wilk’s test. Means were compared using the Wilcoxon rank sum test or Student t-test (with Levene’s test for equality of variances) depending on the distribution of the data. Proportions were compared using the Chi-square test, or Fisher’s Exact test when the observed frequencies were less than five. A 2-tailed P value of less than 0.05 was considered statistically significant. Kaplan–Meier curves were constructed using Prism (Graphpad software, La Jolla, CA, USA).

RESULTS

901 patients underwent orthotopic heart transplantation during the period of study, including 12 patients with cardiac sarcoidosis and 889 patients without cardiac sarcoidosis. Baseline characteristics are described in table 1. The mean age of patients with cardiac sarcoidosis was lower than those without (41.2 years versus 48.5 years, $p=0.0263$). All other baseline characteristics were similar, including recipient height, recipient weight, recipient body mass index, transplant listing status, trans-pulmonary pressure gradient, serum Creatinine and ischaemic time. No cardiac sarcoidosis patients received mechanical circulatory support as a bridge to transplantation.

Individual clinical details for the 12 patients with cardiac sarcoidosis that underwent heart transplantation are presented in table 2. A pre-transplant diagnosis of cardiac sarcoidosis was established in 4 patients due to lung ($n=3$) and cutaneous ($n=1$) involvement. In the remaining 8 patients, the pre-transplant diagnosis was dilated cardiomyopathy and sarcoidosis was only diagnosed by pathological examination of the explanted heart. An example of a typical non-caseating granuloma in an explanted

Table 1. Baseline and operative characteristics stratified by diagnosis

Baseline characteristics	Sarcoidosis (n=12)	Non sarcoidosis (n=889)	p-value
Male	9 (75%)	691 (78%)	NS
Age (years)	41.2 ± 10	48.5 ± 11.3	p=0.0263
Height (cm)	170 ± 8	172 ± 9	NS
Weight (kg)	73 ± 11	74 ± 13	NS
Body mass index (kg/m ²)	25 ± 3	25 ± 4	NS
Pre-transplant serum Creatinine (µmol/L)	129 ± 17	126 ± 82	NS
Pre-transplant mechanical circulatory support	0 (0%)	58 (6.5%)	NS
Pre-operative transpulmonary pressure gradient	7 ± 3	8 ± 3	NS
Listing status			
Routine	11 (92%)	778 (88%)	NS
Urgent	1 (8%)	111 (12%)	
Ischaemic time	170 ± 45	188 ± 62	NS

Table 2. Clinical details of patients with cardiac sarcoidosis

Case	Gender	Age	Pre-CTx diagnosis	Pre-CTx extra-cardiac sarcoidosis	Follow up	Vital status or cause of death
1	M	42	N	N	91 months	Alive
2	M	44	Y	Pulmonary	90 months	Alive
3	M	41	N	N	59 months	Alive
4	F	56	N	N	43 months	Alive
5	M	58	Y	Pulmonary	37 months	Alive
6	M	42	Y	Skin	31 months	Alive
7	M	40	Y	Pulmonary	20 months	Alive
8	F	63	N	N	5 months	Sudden cardiac death
9	M	41	N	N	55 months	Renal failure
10	M	62	N	Gastrointestinal	70 months	Cardiac allograft vasculopathy
11	F	29	N	N	288 months	Alive
12	M	48	N	N	203 months	Alive

heart is provided in Figure 1. Two patients had pre-transplant arrhythmias, one patient had high grade atrio-ventricular block and one patient had both high grade atrio-ventricular block and ventricular tachycardia. Both of these patients had a pre-transplant diagnosis of sarcoidosis with involvement of other organ systems.

Immunosuppressive treatment included 1, tacrolimus, sirolimus or cyclosporine, 2, azathioprine or mycophenolate mofetil, and 3, corticosteroids that were gradually tapered to 5 mg daily by the end of the first year and stopped if possible. Details of immunosuppressive therapy for each patient with cardiac sarcoidosis at the end of year one and year five are provided in table 3. Possible complications of immunosuppressive treatment included renal failure

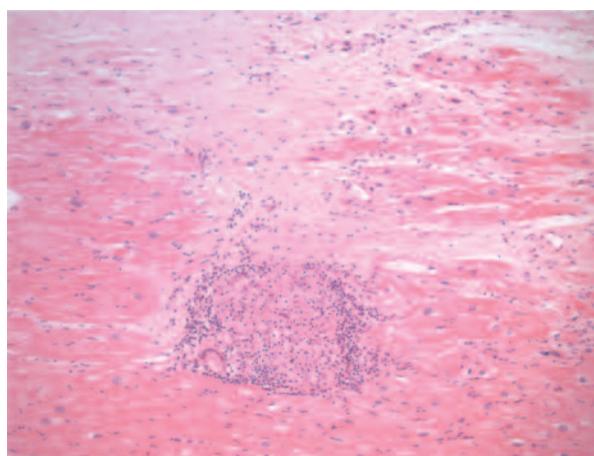
**Fig. 1.** Photomicrograph of typical granuloma seen in the explanted heart of patient with cardiac sarcoidosis

Table 3. Morbidity during observed follow-up in patients transplanted for cardiac sarcoidosis

Case	CAV grade year 1-2	CAV grade year 3-5	Serum Creatinine year 1-2 ($\mu\text{mol/L}$, median)	Serum Creatinine year 3-5 ($\mu\text{mol/L}$, median)	Immunosuppression year 1 end	Immunosuppression year 5 end	Episode of acute cellular rejection (grade)
1	1	1	128	131	T, M, P 2.5 mg	T, M	Y (2R)
2	0	0	96	99	T, M, P 5 mg	T, M, P 5 mg	N
3	0	0	116	128	T, M, P 2.5 mg	T, M, P 5 mg	N
4	0	N/A	79	N/A	T, M	N/A	N
5	1	N/A	98	N/A	T, M, P 5 mg	N/A	N
6	0	N/A	94	N/A	T, M, P 5 mg	N/A	N
7	1	N/A	111	N/A	T, M, P 5 mg	N/A	N
8	N/A	N/A	N/A	N/A	N/A	N/A	Y (2R)
9	No morbidity data available for this patient; clinical records unavailable due to time elapsed since patient death						
10	0	0	161	185	C, M, P 5mg	S, P 5 mg	N
11	0	0	104	118	C, A	C, A	N
12	0	0	198	125	C, P 5 mg	C, M, P 5 mg	Y (2R)

Cardiac Allograft Vasculopathy (CAV) grade as per 2010 International Society for Heart and Lung Transplantation standardized nomenclature; Acute Cellular Rejection grade as per 2005 International Society for Heart and Lung Transplantation standardized nomenclature; Immunosuppression abbreviations T=Tacrolimus, C=Ciclosporin, S=Sirolimus, M=Mycophenolate Mofetil, A=Azathioprine, P=Prednisolone, N/A=Not available at this time

requiring haemodialysis (n=1) and primary cytomegalovirus infection (n=1). All patients underwent regular endomyocardial biopsy during the first year. Three cardiac sarcoidosis patients were treated for acute cellular rejection with intravenous corticosteroids during their first year after transplantation.

Three cardiac sarcoidosis patients died during follow-up. One patient died suddenly 5 months post-transplant and post mortem examination showed severe coronary vasculitis thought to be due to acute rejection. A second patient died 6 years post-transplant and post-mortem examination showed CAV. Interestingly, CAV was not seen on invasive coronary angiography undertaken two years before death. A third patient died 4 years post-transplant due to end-stage renal failure. This patient received haemodialysis before death but details of morbidity are not included in table 3 as paper clinical records were destroyed at 15 years after death. Nine patients (75%) are still alive after a median follow-up of 57 months (range 20 to 288 months), including all four patients that had a pre-transplant diagnosis of sarcoidosis and extra-cardiac involvement.

In total, post-transplant survival for cardiac sarcoidosis patients was 100% at 30 days, 92% at one year and 83% at five years. In comparison, post-transplant survival for patients with an alternate diagnosis was 91% at 30 days, 83% at one year and 64% at five years. There was no difference in observed survival between patients with and without

cardiac sarcoidosis by Kaplan-Meier analysis (Figure 2, log rank test $P=0.3772$).

No recurrence of the sarcoidosis in the allograft was seen during 1001 months of follow up. No patients developed *de novo* extra-cardiac sarcoidosis or progressive extra-cardiac sarcoidosis. Three cardiac sarcoidosis patients had post-transplant arrhythmias. One patient had high grade AV block within two weeks of transplantation and a permanent pacemaker was implanted. A second patient had an atrial tachycardia at six years after transplantation and underwent curative radio-frequency ablation. A third

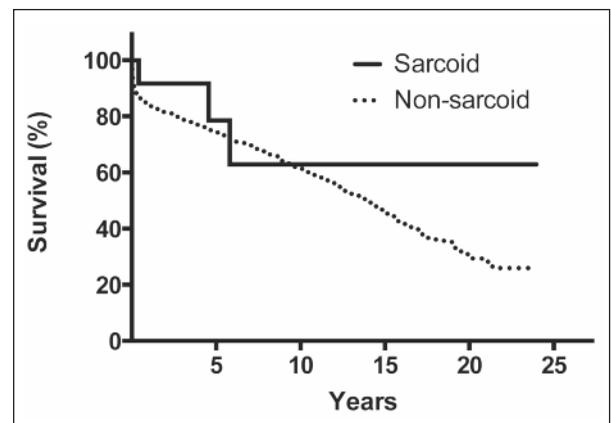


Fig. 2. Kaplan Meier curve of post-transplant survival for patients with cardiac sarcoidosis (solid line) and without cardiac sarcoidosis (hatched line)

patient developed atypical atrial flutter at sixteen years after transplantation and was managed with medical therapy. No patients had documented ventricular arrhythmias after transplantation. Renal function deteriorated in four cardiac sarcoidosis patients after transplantation, although only one of these patients went on to require renal replacement therapy. Where available, median serum Creatinine at years 1-2 and years 3-5 is described in table 3. Mild cardiac allograft vasculopathy was seen in 3 of 10 patients that underwent invasive coronary angiography at 1-2 years and 1 of 6 patients that underwent repeat invasive angiography at 3-5 year. No patients with cardiac sarcoidosis have developed moderate or severe cardiac allograft vasculopathy during follow-up. Finally, no cardiac sarcoidosis patients underwent re-transplantation or developed malignancy during follow-up.

DISCUSSION

In a series of consecutive patients that underwent heart transplantation for cardiac sarcoidosis at a single center in the United Kingdom, excellent post-transplant outcomes with survival of 92% at one year and 83% at five years were observed. There was no difference in survival between patients that underwent heart transplantation for cardiac sarcoidosis and those that underwent heart transplantation for an alternate diagnosis. In contrast to previous case reports, we did not encounter recurrent sarcoidosis in the transplanted heart or progression of extra-cardiac sarcoidosis (12-14). Although this was an observational study, the two groups had similar baseline characteristics with the exception of age.

Three previous observational studies have described survival in patients that underwent heart transplantation for cardiac sarcoidosis. In a retrospective analysis of 38,230 patients in the United Network for Organ Sharing (UNOS database), of whom 65 patients had cardiac sarcoidosis, one year post transplant survival was 87.7% for patients with cardiac sarcoidosis and 84.5% for patients with an alternate diagnosis ($p=0.03$) (8). However, there were significant differences in several baseline characteristics (gender, ethnicity, listing status) and the presence of extra-cardiac sarcoidosis was not described. In addition, the study did not describe

whether cardiac sarcoidosis was apparent before transplantation or only identified at pathological examination of the explanted heart.

In a series of 1069 patients at a single United States (US) center, of whom 19 patients had cardiac sarcoidosis, there was no significant difference in five-year post transplant survival for patients with cardiac sarcoidosis (79%) and patients with an alternate diagnosis (83%). In addition, there were no significant differences in freedom from treated rejection at one year, cardiac allograft vasculopathy at five years and nonfatal major adverse cardiac events at five years (myocardial infarction, heart failure, stroke, need for pacemaker or defibrillator) (11). In this series, 63% of patients had a definite diagnosis of cardiac sarcoidosis before heart transplantation, as proven by endomyocardial biopsy (21%) or extra-cardiac sarcoidosis (42%). However, the study did not report baseline characteristics and this represents a potential source of bias.

Concerns were raised about post-transplant outcomes for patients with cardiac sarcoidosis in a third series of 825 patients at a single US center, of whom 14 patients had cardiac sarcoidosis (9). Kaplan-Meier analysis showed lower post-transplant survival in patients with cardiac sarcoidosis ($p=0.0942$). One year survival was 78.5% for patients with cardiac sarcoidosis and 87.2% for those with an alternate diagnosis. Five-year survival was 52.4% for patients with cardiac sarcoidosis and 76.2% for those with an alternate diagnosis. The two groups had similar baseline characteristics, with the exception of gender and ethnicity. In this study, 42.9% of patients were diagnosed with cardiac sarcoidosis before transplantation and in retrospect, 50% of patients had evidence of pulmonary sarcoidosis at the time of transplantation. Patients with pulmonary sarcoidosis fared particularly badly after heart transplantation, despite triple immunosuppressive therapy with calcineurin inhibitors, mycophenolate and corticosteroids.

Where do these data leave advanced heart failure cardiologists who are being referred patients with cardiac sarcoidosis for consideration of heart transplantation? It appears that carefully selected patients with advanced heart failure due to cardiac sarcoidosis have an acceptable outcome after transplantation. However, careful selection is essential because certain baseline characteristics such as pulmonary involvement may confer an adverse prognosis after heart trans-

plantation. Cardiologists should be aware that reported experience of transplantation for cardiac sarcoidosis largely represents isolated cardiac sarcoidosis that was only diagnosed at pathological examination of the explanted heart. When this situation arises, it may be sensible to undertake systematic search for evidence of extra-cardiac sarcoidosis at the start of long-term follow up. Finally, cardiologists should consider including long-term corticosteroid in the immunosuppressive regime of patients that have been transplanted for cardiac sarcoidosis (12,15). The rationale for this suggestion is that corticosteroids remain the mainstay of treatment for most patients with sarcoidosis. Randomized controlled trials in pulmonary sarcoidosis have examined use of immunosuppressive medications such as Calcineurin inhibitors, but these have only been used in conjunction with corticosteroid therapy and do not improve outcomes compared with corticosteroids alone (16,17).

LIMITATIONS

In common with previous publications, this is an observational study that includes small numbers of patients with cardiac sarcoidosis. Bias is introduced by differences in baseline characteristics (age) and there are likely to be significant differences in unmeasured baseline characteristics. The majority of cardiac sarcoidosis cases were diagnosed at pathological examination of explanted heart, rather than before transplantation. These patients may have isolated cardiac sarcoidosis and their post-transplant survival may differ from patients with clinically apparent cardiac sarcoidosis and extra-cardiac involvement. Indeed, one might question the significance of non-caseating granulomata in the explanted heart (18). Finally, selection bias is inevitable in any series of transplanted patients because individuals with more severe multi-system disease are less likely to be referred for assessment, less likely to be listed for transplantation and less likely to survive on the waiting list for transplantation.

CONCLUSION

In our consecutive series of patients with cardiac sarcoidosis that underwent heart transplantation at a

single center in the United Kingdom, observed survival was 92% at one year and 83% at five years. There was no difference in survival between patients that underwent transplantation for cardiac sarcoidosis and those that underwent transplantation for an alternate diagnosis. With the exception of age, all baseline characteristics were well matched between the two groups compared. In contrast to previous case reports, we did not encounter recurrent sarcoidosis in the transplanted heart or progression of sarcoidosis in other organ systems. However, these observations should be interpreted with caution. Only 33% of patients received a diagnosis of sarcoidosis before pathological examination of the explanted heart, and this group was highly selected for suitability for heart transplantation.

ACKNOWLEDGEMENTS

EKT is supported by grant by the Hellenic Cardiological Society. The authors would like to thank Marie Davies and Derek Skinner for their help with extracting data from the Papworth hospital transplantation database.

REFERENCES

1. Sekhri V, Sanal S, Delorenzo LJ, Aronow WS, Maguire GP. Cardiac sarcoidosis: a comprehensive review. *Arch Med Sci* 2011; 7 (4): 546-54.
2. Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med* 2001; 164 (10 Pt 1): 1885-9.
3. Pierre-Louis B, Prasad A, Frishman WH. Cardiac manifestations of sarcoidosis and therapeutic options. *Cardiol Rev* 2009; 17 (4): 153-8.
4. Roberts WC, McAllister HA, Ferrans VJ. Sarcoidosis of the heart. A clinicopathologic study of 35 necropsy patients (group 1) and review of 78 previously described necropsy patients (group 11). *Am J Med* 1977; 63 (1): 86-108.
5. Tavora F, Cresswell N, Li L, Ripple M, Solomon C, Burke A. Comparison of necropsy findings in patients with sarcoidosis dying suddenly from cardiac sarcoidosis versus dying suddenly from other causes. *Am J Cardiol* 2009; 104 (4): 571-7.
6. Kandolin R, Lehtonen J, Graner M, et al. Diagnosing isolated cardiac sarcoidosis. *J Intern Med* 2011; 270 (5): 461-8.
7. Dubrey SW, Falk RH. Diagnosis and management of cardiac sarcoidosis. *Prog Cardiovasc Dis* 2010; 52 (4): 336-46.
8. Zaidi AR, Zaidi A, Vaitkus PT. Outcome of heart transplantation in patients with sarcoid cardiomyopathy. *J Heart Lung Transplant* 2007; 26 (7): 714-7.
9. Akashi H, Kato TS, Takayama H, et al. Outcome of patients with cardiac sarcoidosis undergoing cardiac transplantation - single-center retrospective analysis. *J Cardiol* 2012; 60 (5): 407-10.
10. Chang T-I, Chi N-H, Chou N-K, et al. Isolated cardiac sarcoidosis

- in heart transplantation. *Transplant Proc* 2012; 44 (4): 903-6.
11. Perkel D, Czer LSC, Morrissey RP, et al. Heart transplantation for end-stage heart failure due to cardiac sarcoidosis. *Transplant Proc* 2013; 45 (6): 2384-6.
 12. Oni AA, Hershberger RE, Norman DJ, et al. Recurrence of sarcoidosis in a cardiac allograft: control with augmented corticosteroids. *J Heart Lung Transplant* 1992; 11 (2 Pt 1): 367-9.
 13. Yager JEE, Hernandez AF, Steenbergen C, et al. Recurrence of cardiac sarcoidosis in a heart transplant recipient. *J Heart Lung Transplant* 2005; 24 (11): 1988-90.
 14. Belziti CA, Maldonado S, Vulcano N, et al. Cardiac Sarcoidosis: Recurrence in a Heart Transplant Recipient. *Rev Argent Cardiol* 2010; 78: 358-60.
 15. Baughman RP, Nunes H. Therapy for sarcoidosis: evidence-based recommendations. *Expert Rev Clin Immunol* 2012;8 (1): 95-103.
 16. Paramothayan NS, Lasserson TJ, Jones PW. Corticosteroids for pulmonary sarcoidosis. *Cochrane Database Syst Rev* 2005; (2): CD001114.
 17. Paramothayan S, Lasserson TJ, Walters EH. Immunosuppressive and cytotoxic therapy for pulmonary sarcoidosis. *Cochrane Database Syst Rev* 2006; (3): CD003536.
 18. Yazaki Y. The diagnostic dilemma of isolated cardiac sarcoidosis. *Intern Med* 2013; 52 (1): 1-2.