Comparison of Clinical and Morphologic Findings in Patients With Cardiac Sarcoidosis Severe Enough to Warrant Heart Transplantation in Those With -vs- Those Without Non-Caseating Granulomas in the Explanted Heart (Burnt-Out Sarcoid)

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Can cardiac sarcoidosis with heart failure severe enough to warrant orthotopic heart transplantation (OHT) be present without non-caseating granulomas in the explanted heart? The objective is to compare clinical and morphological features in patients with cardiac sarcoidosis severe enough to warrant OHT with -vs-without non-caseating granulomas in the explanted heart. The study was conducted at Baylor University Medical Center in Dallas, Texas. From a total of 671 explanted hearts examined from 1993 to 2018, twenty-five (4%) had gross morphologic features characteristic of cardiac sarcoidosis. At the time of OHT, the patients ranged in age from 50 to 69 years [mean 57]. Cardiac sarcoidosis was diagnosed before OHT in 3 (12%) patients, by percutaneous biopsy of the heart in 2 patients and by histologic examination of the "left ventricular core" in 1 patient who had a left ventricular assist device inserted, and, by examination of the native heart after OHT in the remaining 22 (88%) patients. Of the 25 patients, 16 (64%) had typical sarcoid non-caseating granulomas in the explanted heart, and 9 (36%) had no granulomas in the explanted heart. Comparison of certain clinical and morphologic features in the group with -vs- the group without cardiac granulomas showed no significant differences. In conclusion, of patients with cardiac sarcoidosis severe enough to warrant OHT, some have typical non-caseating granulomas in the explanted heart and some do not. The clinical and gross morphologic features of those with and those without cardiac granulomas are similar. **(Am J Cardiol 2019;124:599−603)**

Sarcoidosis has usually been defined by the presence of non-caseating granulomas containing multinucleated giant cells, epithelioid cells and lymphocytes in one or more body organs. When sarcoidosis attacks an organ, scar tissue develops in the areas of the granulomas and eventually it appears that the scar tissue can obliterate all evidence of previous inflammation, including the giant cells. This scenario appears to occur in cardiac sarcoidosis. Herein, we describe certain clinical and cardiac morphologic findings in 25 patients who had orthotopic heart transplant (OHT) for what proved to be cardiac sarcoidosis. We compared clinical and morphologic features of the cases with to those without non-caseating granulomas in the explanted hearts.

Methods

Since March 1993 one of us (WCR) has examined all specimens excised by cardiac surgeons at Baylor University Medical Center (BUMC) and submitted the report on each. From March 1993 through December 2018, we examined 671 native hearts excised at the time of OHT at BUMC. All hearts were opened and sections made by WCR. The weights of the hearts were all done by the same investigator after opening the chambers, removing any excess tissue (parietal pericardium for example), and incising the aorta and pulmonary trunk about 2 cm cephalad to the sino-tubular junction. The hearts were weighed within one week after their fixation in formaldehyde. Photographs were prepared on virtually all the explanted hearts, all of which have been retained. Of these 671 native hearts examined since 1993, twenty-five (4%) had gross morphologic features characteristic of cardiac sarcoidosis. Histologic sections were prepared in each heart, and stained by both hematoxylin/eosin and trichrome. At least 5 sections of myocardium were prepared in each case: 4 from the ventricles and 1 from the atria. All sections were examined by WCR. Photomicrographs were prepared from many of the cases. After examination of the heart and before submitting the final pathology report, the medical records in each case were examined.

Results

Of the 25 cases, 16 (64%) had typical sarcoid non-caseating granulomas in the explanted heart, and 9 (36%) had no granulomas in the explanted heart. Comparison of

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0002-9149/
https://doi.org/10.1016/j.amjcard.2019.05.020

certain clinical and gross morphologic features in the group with -vs- the group without cardiac granulomas showed no significant differences (Table 1). Pertinent data in each of the 25 patients is tabulated in Table 2. Three patients (cases #2, #11 and #18 Table 2) had left ventricular assist devices inserted before OHT and all 3 had granulomas in the excised "left ventricular core", including one (case #18, Table 2) who did not have granulomas in the explanted heart. Of the 9 patients without granulomas in the explanted heart, 3 previously had morphologic proof of cardiac sarcoidosis (2 by percutaneous biopsies of the heart [cases #19 and #22, Table 2] and one by examination of the portion of left ventricular free wall excised to insert a left ventricular assist device [case #18, Table 2].) Each of these 3 patients in whom cardiac sarcoidosis was proven by tissue examination before OHT were treated with corticosteroid therapy (cases #18, #19, and #22, Table 2). Additionally, two of the remaining 22 patients in whom the diagnosis of cardiac sarcoidosis was not proven before OHT also were treated with corticosteroid drugs because of biopsy proved pulmonary sarcoidosis (Cases #2 and #24, Table 2). Two patients (case #4 and #7, Table 2) had significant coronary narrowing, one (case #4, Table 2) of whom had coronary artery bypass grafting. Electrocardiographic features before OHT in each of the 25 patients are tabulated in table 3.

Table 1
Comparison in patients with clinical and morphologic findings of cardiac sarcoidosis severe enough to warrant heart transplantation in those with -vs- those without non-caseating granulomas in the explanted heart

Variable	Total (n = 25)	Cardiac granulomas		p Value
		No (n = 9)	Yes (n = 16)	
Age (years)	57 ± 6	56 ± 9	57 ± 5	0.81
Men	13 (52%)	6 (67%)	7 (44%)	0.41
Women	12 (48%)	3 (33%)	9 (56%)	
White	19 (76%)	6 (67%)	13 (81%)	0.63
Black	6 (24%)	3 (33%)	3 (19%)	
Duration (months), symptoms	72 ± 53	76 ± 65	70 ± 48	0.79
Atrial arrhythmias	7 (28%)	4 (44%)	3 (20%)	0.36
Ventricular arrhythmias	8 (32%)	1 (11%)	7 (47%)	0.18
Bundle branch block				0.28
Left	4 (16%)	1 (11%)	3 (19%)	
Right	10 (40%)	3 (33%)	7 (44%)	
Indeterminate	3 (12%)	0	3 (19%)	
Total 12-lead QRS Voltage (mm)	88 ± 36	99 ± 20	82 ± 41	0.30
Total cholesterol (mg/dl)	150 ± 42	160 ± 47	145 ± 40	0.44
LDL cholesterol (mg/dl)	90 ± 29	96 ± 27	87 ± 30	0.48
Body mass index (Kg/m^2)	28 ± 5	29 ± 7	28 ± 3	0.70
Prior LVAD	3 (12%)	2 (22%)	1 (6%)	0.60
Corticosteroid therapy	5 (24%)	4 (44%)	1 (6%)	0.097
Heart weight (g)				
Men	490 ± 58	491 ± 80	492 ± 51	0.91
Women	423 ± 86	438 ± 141	418 ± 71	0.75
Floating heart	12 (48%)	4 (44%)	8 (53%)	1.00

LDL = low density lipoprotein; LVAD =left ventricular assist device.

Discussion

The present report describes 25 patients who underwent OHT because of chronic severe heart failure resulting from cardiac sarcoidosis: 16 of the patients had classic non-caseating granulomas in the operatively-excised native hearts and 9 had no granulomas in the explanted hearts, although 3 of them had typical granulomas in percutaneous biopsies of heart or in the "left ventricular core" excised at the time of insertion of left ventricular assist device. Comparison of various clinical and gross morphologic features of the 16 patients with granulomas in the explanted hearts to the 9 patients without disclosed no significant differences.

Typical gross and histologic features of cardiac sarcoidosis severe enough to warrant OHT include focal but extensive scars in the walls of both left and right ventricles and ventricular septum.[1–8] Scars in the atrial walls are infrequent.[5] The focal scars in the right ventricular wall are usually transmural; those involving the left ventricular wall may also be transmural but often they are only subepicardial, the opposite of what occurs in hearts of patients with coronary heart disease, which is subendocardial or transmural or both but not subepicardial.[9] The ventricular walls are more often thinner than normal rather than thicker than normal. The ventricular cavities are severely dilated (unless a left ventricular assist device had been inserted earlier). Histologically, the non-caseating granulomas are typically located within the scars and numerous ones are present in some scars. In most patients some ventricular wall scars contain granulomas and others do not. The numbers of nuclei present in the giant cells may exceed 50. Lymphocytes also are present.

How can we be certain that the 9 patients without non-caseating granulomas in the explanted hearts have cardiac sarcoidosis? In 3 of these 9 patients an earlier percutaneous biopsy (in 2) or examination of the portion of left ventricular wall excised to insert a left ventricular assist device (in 1) did indeed contain non-caseating granulomas. The interval from this tissue examination to the OHT in these 3 patients was 0.1, 7, and 53 months, respectively. Another supporting factor was that many of the ventricular wall scars in the 16 patients with granulomas present in the explanted heart also had ventricular-wall scars without any granulomas. The latter observation suggests it would not be a "stretch" for all the scars to eventually be devoid of granulomas. Three of the 9 patients without granulomas in the explanted hearts were treated with cortico-steroid therapy, a known cause of converting non-caseating granulomas into scars without granulomas.[1] (Each of the 3 patients in whom the diagnosis was made by examination of cardiac tissue some time before the OHT were treated with prednisone.)

The positive features of this report are the following: (1) no previous report has emphasized that cardiac sarcoidosis may be present without non-caseating granulomas being present in the heart. (2) No previous study has compared clinical and gross morphologic findings in the patients with to those without non-caseating granulomas in the heart.

Limitations of the present study include the following: (1) perhaps not enough histologic sections of myocardium were studied. (We examined at least 4 large

Table 2
Pertinent clinical and morphological findings in 25 patients who had orthotopic heart transplantation for cardiac sarcoidosis

Case	Age (years)	Sex	Race	Duration of symptoms before OHT (months)	BMI (Kg/m^2)	TC (mg/dl)	LDL (mg/dl)	CI (l/min/m^2)	P-Rx	Clinical cardiac diagnosis	ICD	HW (g)	Heart floats	G	Location of granulomas		
															RV	VS	LV
1	50	F	B	132	25	124	74	–	0	IDC	+	440	0	+	1+	3+	3+
2	52	M	W	192	28	172	108	1.6	+	IDC*	0	440	0	+	1+	2+	1+
3	52	F	B	50	31	166	64	2.3	0	IDC	+	440	0	+	1+	3+	3+
4	53	M	W	12	27	188	112	1.6	0	IDC	0	555	+	+	3+	3+	3+
5	54	F	W	46	26	74	46	1.8	0	IDC	0	425	0	+	3+	3+	3+
6	54	M	W	108	30	210	134	-	0	IDC	0	511	-	+	3+	3+	3+
7	56	F	W	11	26	143	118	–	0	IDC	0	450	+	+	1+	3+	3+
8	57	F	W	46	30	138	94	1.4	0	IDC	0	380	0	+	3+	3+	3+
9	58	F	W	60	27	229	147	2.2	0	IDC	+	560	+	+	3+	3+	3+
10	58	M	W	48	25	114	64	1.2	0	IDC	0	420	0	+	3+	3+	3+
11	59	F	B	72	26	134	69	1.3	0	IDC	+	370	0	+	1+	2+	1+
12	60	F	W	36	28	130	93	1.2	0	IDC	0	401	+	+	1+	3+	3+
13	61	F	W	120	25	119	60	1.2	0	IDC	0	300	+	+	3+	3+	3+
14	63	M	W	84	33	109	52	1.6	0	IDC	+	470	+	+	3+	3+	3+
15	63	M	W	48	24	157	86	1.7	0	IDC	0	540	+	+	3+	3+	3+
16	67	M	W	48	30	116	70	1.6	0	IDC	0	510	+	+	3+	3+	3+
17	40	F	W	11	45	107	78	1.4	0	IDC	0	370	0	0	0	0	0
18	50	M	W	36	28	185	119	1.7	+	CS	+	605	0	0	0	0	0
19	53	M	W	60	31	233	120	1.9	+	CS	0	535	0	0	0	0	0
20	54	F	B	100	24	191	108	1.8	0	IDC	0	345	0	0	0	0	0
21	57	M	W	36	30	119	82	1.2	0	IDC	0	420	+	0	0	0	0
22	59	M	W	48	28	–	–	–	+	CS	+	420	+	0	0	0	0
23	62	F	B	216	19	182	129	1.5	0	IDC	+	600	0	0	0	0	0
24	65	M	B	139	29	160	82	–	+	IDC	+	475	+	0	0	0	0
25	69	M	W	36	23	101	50	1.3	0	IDC	0	475	+	0	0	0	0

AB = black; BMI = body mass index; CI = cardiac index; CS = cardiac sarcoidosis; F = female; G = granuloma; HW = heart weight; I = indirect; ICD = intracardiac defibrillator; IDC = ischemic dilated cardiomyopathy; L = left; LDL = low-density lipoprotein; LV = left ventricle; M = male; OHT = orthotopic heart transplant; P = prednisone Rx; R = right; RV = right ventricle; TC = total cholesterol; VS = ventricular septum; W = white.

* Because the patient had biopsy-proven pulmonary sarcoid, the patient clinically was considered to have cardiac sarcoid as well, but a cardiac biopsy done before the OHT was negative for sarcoid.

Table 3
Electrocardiographic findings before orthotopic heart transplantation in 25 patients with cardiac sarcoidosis

Case	Paced	QRS amplitude in each electrocardiographic lead (mm)												Total 12-lead QRS voltage (mm)	Arrhythmias		BBB (Type)	CHB	Prolonged QT Interval
		I	II	III	aVR	aVL	aVF	V1	V2	V3	V4	V5	V6		A (Type)	V (Type)			
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
1	+	2	23	13	6	7	28	4	12	16	20	18	12	161	0	0	+ (NS)	+	0
2	0	14	12	8	13	11	7	12	8	8	18	22	22	155	0	0	+ (R)	0	0
3	+	5	5	5	5	2	8	6	7	7	5	5	7	67	0	+ (VPC)	+ (L)	0	0
4	+	4	12	9	6	3	9	7	7	3	7	10	9	86	0	+ (VPC)	+ (R)	+	0
5	+	4	4	5	2	8	4	–	–	–	–	–	–	–	0	0	0	+	0
6	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	-	-
7	+	4	7	8	5	6	8	4	8	4	5	7	7	73	0	+ (VT)	0	0	0
8	0	5	1	6	3	6	4	5	9	5	4	2	2	52	+ (AT)	0	+ (R)	0	0
9	0	8	8	15	3	11	12	5	7	4	4	6	6	89	0	0			
	+	3	3	4	2	3	3	3	7	3	3	4	4	69	0	0	+ (R)	0	0
10	+	9	9	6	4	4	6	5	3	8	8	8	7	77	0	0	+ (L)	0	0
11	0	11	11	17	8	14	13	9	5	9	12	16	19	144	0	0			
	+	10	12	19	8	14	15	8	9	10	13	15	14	147	0	0	+ (R)	+	0
12	0	5	3	4	5	7	3	3	7	4	6	2	5	54	+ (AF)	+ (VPC)	0	0	0
13	+	4	4	5	3	6	4	4	10	5	7	7	8	72	0	0	+ (R)	+	+
14	+	5	12	8	8	5	10	8	9	14	10	9	5	103	0	+ (VPC)	+ (L)	+	0
15	0	8	6	3	6	6	4	9	10	13	18	22	29	134					
	+	5	8	11	5	6	11	2	4	12	17	11	3	95	+ (AF)	+ (VPC)	+ (R)	0	0
16	+	4	5	7	2	5	5	2	2	6	5	3	1	47	0	+ (VT)	+ (NS)	+	0
17	0	18	6	13	6	13	7	6	6	6	6	5	6	98	+ (APC)	+ (VPC)	0	0	0
18	0	7	11	14	5	9	12	6	14	19	7	10	7	121	+ (APC)	0	+ (L)	0	0
19	+	7	7	10	4	8	9	5	7	5	6	7	6	81	0	0	0	+	0
20	0	3	7	7	4	4	6	4	8	11	9	12	14	89	0	0	0	0	+
21	0	5	8	4	5	4	6	7	10	28	26	22	6	131	+ (APC)	0	+ (R)	0	+
22	0	4	1	5	4	3	4	–	–	–	–	–	–	–	0	0	0	0	0
23	0	10	11	10	7	7	7	10	9	7	9	10	10	107	0	0	+ (R)	0	0
24	0	5	7	5	6	4	5	5	4	5	7	10	11	74	+ (AF)	0	+ (R)	0	0
25	0	10	5	6	6	11	12	11	6	4	4	12	4	91	0	0	0	0	0

A = atrial; AF = atrial fibrillation; APC = atrial premature complexes; AT= atrial tachycardia; BBB = bundle branch block; CHB = complete heart block; L = left; NS = non-specific; R = right; V= ventricular; VPC = ventricular premature complexes; VT = ventricular tachycardia.

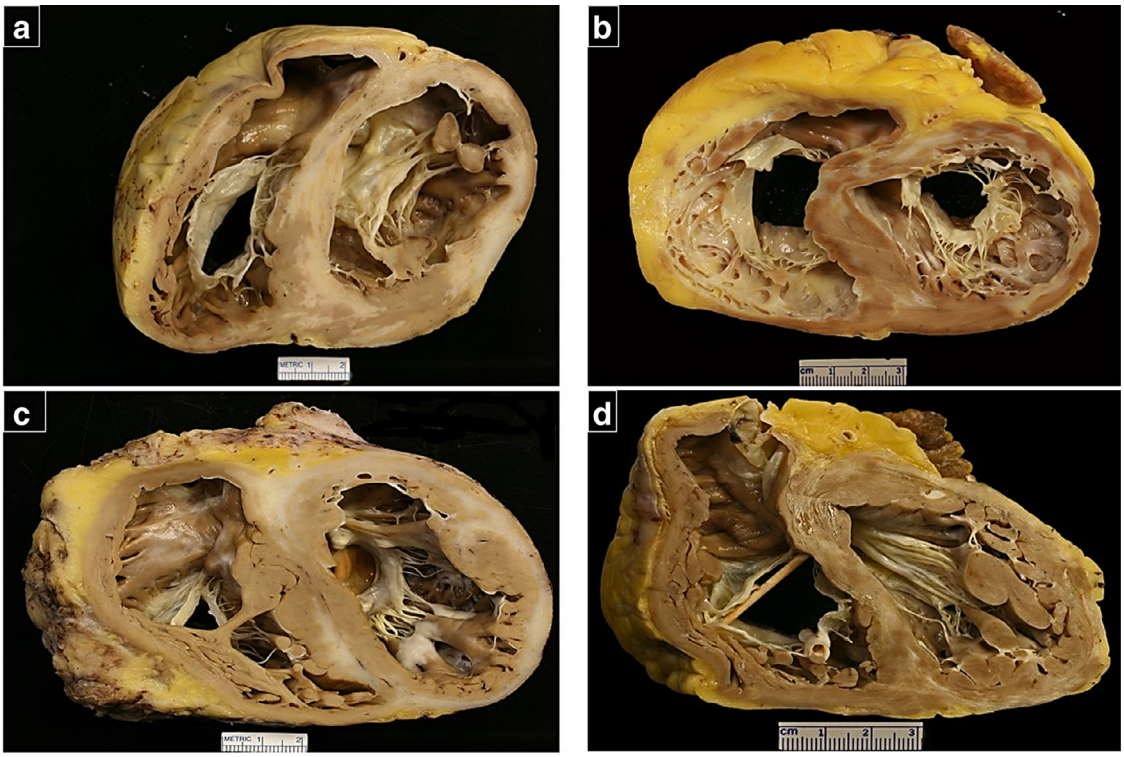

Figure 1. Shown here are basal portions of the heart in 4 patients, 2 of whom (*a* and *c*) had granulomas in the explanted heart and 2, (*b* and *d*) did not. (*a*) patient #5 (Table 2); (*b)* patient #23 (Table 2); *(c*) patient #12 (Table 2); *d*) patient #20 (Table 2). Both ventricles are dilated in each of these 4 patients. Portions of the tricuspid and mitral valves are visible in all 4 patients. The white areas of right ventricular free wall, ventricular septum and left ventricular free wall represent sites of scarring, some of which contained non-caseating granulomas and some of which did not.

[endocardium-to-epicardium] sections of the ventricular walls in all 25 patients and far more [up to 20] in a few patients.); (2) perhaps the 9 patients without tissue proof of cardiac sarcoidosis *in the explanted hearts*, namely the presence of non-caseating granulomas, did not have cardiac sarcoidosis. We believe this scenario to be highly unlikely because 3 of the 9 patients had earlier proof of cardiac sarcoidosis (biopsy or left ventricular "core" examination), and, additionally, we know of no other cardiac condition that even remotely resembles the full-blown morphologic features of cardiac sarcoidosis (Figures 1 and 2).

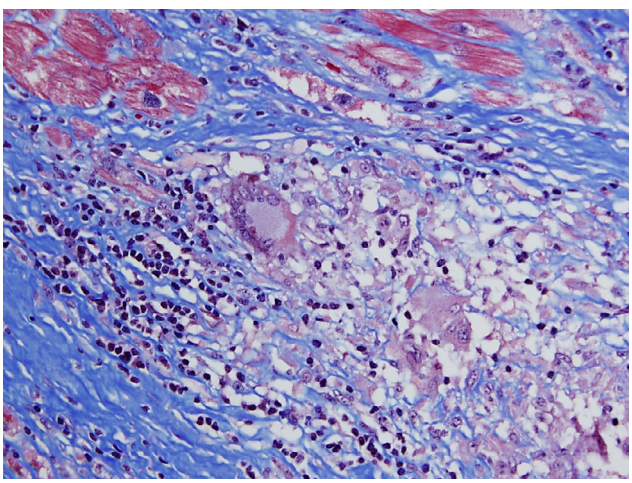

Figure 2. Photomicrograph of a portion of left ventricular free wall in patient #16 (Table 2). The myocardial wall is partially replaced by a dense fibrous tissue which stains blue within which is a sarcoid granuloma. Trichrome stain, original magnification × 40.

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