Case Reports

Right Ventricular Sarcoidosis:

Is It Time for Updated Diagnostic Criteria?

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A 55-year-old woman with a history of complete heart block, atrial flutter, and progressive right ventricular failure was referred to our tertiary care center to be evaluated for cardiac transplantation. The patient's clinical course included worsening right ventricular dysfunction for 3 years before the current evaluation. Our clinical findings raised concerns about arrhythmogenic right ventricular cardiomyopathy. Noninvasive imaging, including a positron emission tomographic scan, did not reveal obvious myocardial pathologic conditions. Given the end-stage nature of the patient's right ventricular failure and her dependence on inotropic agents, she underwent urgent listing and subsequent heart transplantation. Pathologic examination of the explanted heart revealed isolated right ventricular sarcoidosis with replacement fibrosis. Biopsy samples of the cardiac allograft 6 months after transplantation showed no recurrence of sarcoidosis. This atypical presentation of isolated cardiac sarcoidosis posed a considerable diagnostic challenge. In addition to discussing the patient's case, we review the relevant medical literature and discuss the need for updated differential diagnostic criteria for end-stage right ventricular failure that mimics arrhythmogenic right ventricular cardiomyopathy. ***(Tex Heart Inst J 2014;41(2):203-7)***

Cardiac involvement in systemic sarcoidosis has been reported frequently. Nearly all patients with cardiac sarcoidosis have left ventricular (LV) involvement, and most have predominant LV disease. Few prior reports have highlighted the atypical presentation of cardiac sarcoidosis when it clinically presents as arrhythmogenic right ventricular cardiomyopathy (ARVC). Isolated right ventricular (RV) involvement in cardiac sarcoidosis has rarely been reported. We report the case of a patient who presented with end-stage RV failure from isolated RV sarcoidosis and eventually needed cardiac transplantation. Given the inaccuracy of the currently available invasive and noninvasive tests in detecting RV sarcoidosis, such atypical presentations pose a considerable diagnostic challenge. In this report, we review the medical literature in regard to patients who have presented with predominant RV sarcoidosis, and also summarize the diagnostic approach that could be undertaken for earlier detection of this disease.

Key words: *Arrhythmogenic right ventricular dysplasia/diagnosis; cardiomyopathies/complications; diagnosis, differential; diagnostic techniques, cardiovascular; sarcoidosis/diagnosis/physiopathology; ventricular dysfunction, right/diagnosis/etiology/physiopathology*

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Case Report

A 55-year-old white woman was referred for cardiac-transplant evaluation because of end-stage RV failure. Three years earlier, she had presented with syncope and complete heart block. A 2-dimensional (2D) echocardiogram at that time revealed mildly reduced RV systolic function and borderline LV systolic function (ejection fraction, 0.50–0.55). An electrocardiogram showed complete heart block with atrioventricular (AV) dissociation and a ventricular escape rhythm of 30 beats/min. Coronary angiograms revealed normal coronary arteries. No apparent metabolic or infectious causes explained her signs and symptoms. The diagnosis was idiopathic high-grade AV block in the presence of nonischemic cardiomyopathy, and a permanent pacemaker was implanted.

The patient's only other medical issue was controlled hypertension, treated with lisinopril. Her family medical history was not pertinent. Because of the new diagnosis of borderline low LV ejection fraction, carvedilol therapy was initiated. She did well for 2 years with New York Heart Association (NYHA) functional class II symptoms and then presented with atrial flutter. She underwent successful ablation with an uneventful postprocedural course. During the next 8 months, she exhibited substantial clinical

deterioration from worsening RV failure and tricuspid regurgitation. A diagnosis of ARVC was suspected. She was transferred to our transplantation center for advanced care.

On presentation, the patient had NYHA functional class IV symptoms. Her blood pressure was 90/60 mmHg, her heart rate was 100 beats/min, and she had normal oxygen saturation on room air. Auscultation revealed clear lungs, a soft S_3, and a grade 3/6 pansystolic murmur in the tricuspid area. There was jugular venous distention at approximately 20 cm. She had pulsatile hepatomegaly and 2+ edema in the bilateral lower extremities. A 2D echocardiogram showed preserved LV systolic function, a severely thin and dilated RV, and tricuspid annular dilation with torrential tricuspid regurgitation (Fig. 1). Interventricular septal thickness was normal at 1.1 cm. She underwent intravenous dobutamine-assisted diuresis. Right-sided heart catheterization while she was on 3 μg/kg/min of dobutamine yielded a right atrial pressure of 13 mmHg, an RV pressure of 18/13 mmHg, a pulmonary artery pressure of 18/15 mmHg, a pulmonary capillary wedge pressure of 10 mmHg, and a calculated Fick cardiac index of 1.5 L/min/m^2.

The patient underwent a thallium-gallium scan, a positron emission tomographic-fluorodeoxyglucose (PET-FDG) scan, and a high-resolution chest computed tomographic scan; all results were negative for active inflammation or suggestion of cardiopulmonary sarcoidosis. An extensive rheumatologic evaluation for other non-sarcoid inflammatory processes revealed nothing unusual. The patient's angiotensin-converting enzyme levels were normal. A diagnostic endomyocardial biopsy was considered but was not performed, because it was considered to be a relatively high-risk procedure in the presence of extensive RV dilation and wall-thinning—and, more important, highly unlikely to change the management approach at this late stage of the disease course. In view of the unclear explanation for the patient's subacute deterioration from NYHA class II symptoms to inotropic-dependent RV failure over the preceding 6 to 8 months, she was urgently listed for cardiac transplantation. This procedure was successfully performed a month later.

Gross pathologic examination of the explanted heart revealed severe RV dilation with thinning of the RV free wall (maximal thickness, 1.5 mm), and fibrous and fibro-fatty involvement of at least half of the RV (Fig. 2). On differential diagnosis, this was initially attributed to ARVC. However, and of note, histopathologic analysis yielded an extensive, ongoing, noncaseating granulomatous inflammatory reaction with interstitial fibrosis that involved the RV and right interventricular septum but spared the LV (Fig. 3). Acid-fast and Gomori's methenamine-silver stains for mycobacterial and fungal infections were negative. On the basis of the clinical and pathologic evidence, the final diagnosis was RV cardiac sarcoidosis with replacement fibrosis.

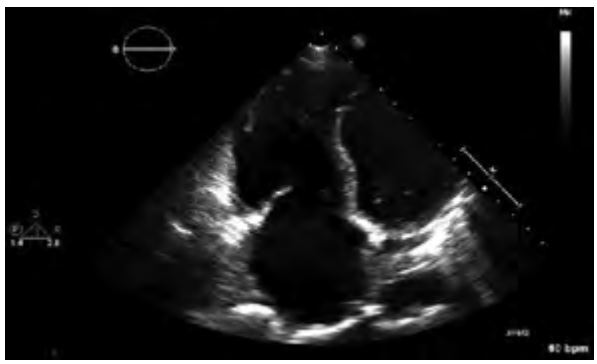

Fig. 1 *Two-dimensional echocardiogram (apical 4-chamber view) shows severe right ventricular, right atrial, and tricuspid annular dilation.*

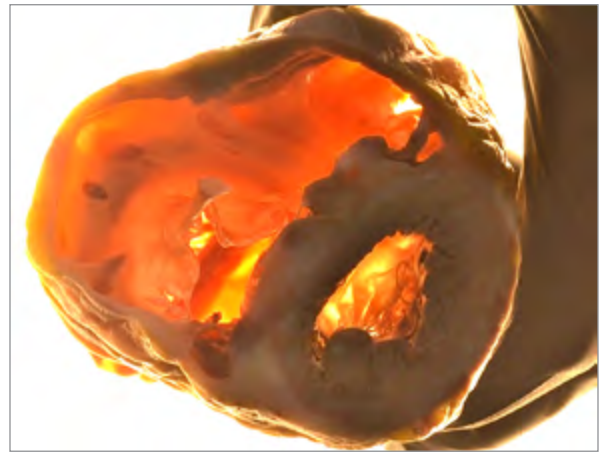

Fig. 2 *Gross pathologic cross-section of the explanted native heart shows marked dilation with fibro-fatty replacement and thinning of the right ventricle.*

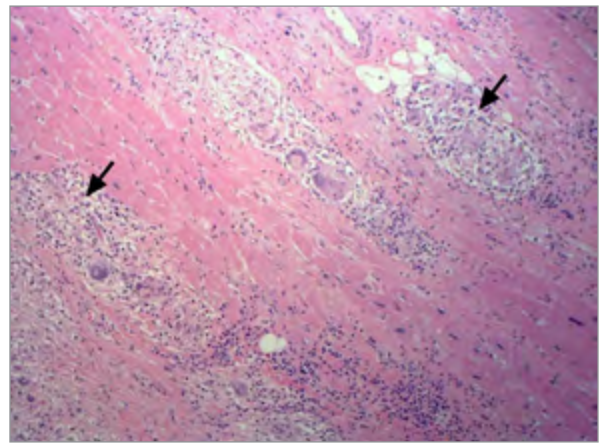

Fig. 3 *Photomicrograph of right ventricular section from the explanted heart shows noncaseating granulomatous inflammation (arrows), consistent with sarcoidosis (H & E).*

The patient did well after transplantation and had no complications. A routine echocardiogram 2 weeks postoperatively showed new, mild LV hypertrophy. No cellular or antibody-mediated rejection was evident during the first year after transplantion, and screening biopsies during this time were negative for recurrent sarcoidosis in the cardiac allograft.

Discussion

Sarcoidosis, a multisystemic granulomatous disorder of unclear cause, often involves the skin, lymph nodes, lungs, heart, central nervous system, and eyes. Although cardiac involvement has been reported in approximately 25% of patients with systemic sarcoidosis, isolated cardiac involvement has occurred even in the absence of systemic disease. Cardiac sarcoidosis typically presents with high-grade AV block, atrial arrhythmias, heart failure, myopericarditis, or sudden cardiac death from ventricular arrhythmias. Nearly all patients have predominant LV disease. However, since 2003, 16 cases of RV sarcoidosis mimicking ARVC have been described (Table I),[1-12] and only 2 patients had isolated RV involvement.[1,6] Our patient had a similar uncommon presentation of cardiac sarcoidosis with isolated RV involvement and LV-sparing that clinically mimicked ARVC.

Atypical presentations of cardiac sarcoidosis are rare and demand a high degree of clinical suspicion. Most often, RV sarcoidosis is confused with ARVC despite the updated 2010 diagnostic task force criteria.[13] Left

TABLE I. Published Reports of Predominant Right Ventricular Cardiac Sarcoidosis

Reference	Age (yr), Sex	Extracardiac	LV Disease	VT	ACE Level	PET-FDG	T/G Scan	CMR	Mimicking ARVC*	Cardiac Biopsy	Death or Transplant**
Shiraishi J, et al.[1] (2003)	59, F	Mediastinal	NA	No	Elevated	NA	Neg	NA	Yes	Pos	No
Ott P, et al.[2] (2003)	37, M	Lungs	No	Yes	NA	NA	NA	Neg	Yes	NA	No
	47, M	No	Yes	Yes	NA	NA	Neg	Neg	Yes	Neg	Death
	33, M	Lung and spleen	Yes	NA	NA	NA	NA	NA	Yes	NA	Death
Froidevaux L, et al.[3] (2007)	44, M	No	Yes	NA	NA	NA	NA	NA	No	Pos	No
Tandri H, et al.[4] (2007)	46, F	Mediastinal	NA	Yes	NA	NA	NA	Neg	Yes	Pos	No
Greif M, et al.[5] (2008)	37, M	No	Yes	Yes	Normal	NA	NA	NA	No	Neg	Transplant
Yared K, et al.[6] (2008)	59, M	Mediastinal	Yes	No	Normal	Pos	NA	Pos	Yes	Pos	No
Vasaiwala SC, et al.[7] (2009)	51, M	No	Yes	Yes	NA	NA	NA	NA	Yes	Pos	No
	44, M	No	Yes	Yes	NA	NA	NA	NA	Yes	Pos	No
	44, M	No	Yes	Yes	NA	NA	NA	NA	Yes	Pos	No
Hiramastu S, et al.[8] (2009)	50, M	NA	Yes	Yes	NA	NA	Pos	Pos	Yes	NA	No
Steger CM, et al.[9] (2009)	41, F	No	Yes	Yes	NA	NA	NA	Neg	Yes	NA	Transplant
Ladyjanskaia, GA, et al.[10] (2010)	44, M	No	Yes	Yes	Elevated	NA	Neg	Neg	Yes	NA	Death
Chia PL, et al.[11] (2012)	35, M	Mediastinal	Yes	Yes	Normal	NA	NA	Pos	Yes	NA	No
Mohsen A, et al.[12] (2012)	38, M	Mediastinal	No	Yes	NA	NA	NA	Pos	Yes	NA	No
Current case	55, F	No	No	No	Normal	Neg	Neg	None	Yes	None	Transplant

ACE = angiotensin-converting enzyme; ARVC = arrhythmogenic right ventricular cardiomyopathy; CMR = cardiac magnetic resonance; F = female; LV = left ventricular; M = male; NA = data not available; Neg = negative study for right ventricular sarcoidosis; PET-FDG = positron emission tomography-^{18}fluorodeoxyglucose; Pos = positive study for right ventricular sarcoidosis; T/G = thallium/gallium; VT = ventricular tachycardia

*ARVC 1994/updated 2010 diagnostic task force criteria[13]

**Before initiation of treatment for cardiac sarcoidosis

ventricular involvement and the presence of systemic sarcoidosis appear to be the most likely findings that distinguish cardiac sarcoidosis from ARVC; however, approximately 10% of patients with ARVC reportedly have concomitant LV involvement.[14] Accordingly, patients who could benefit from treatment might not receive it, because of untimely diagnosis of cardiac sarcoidosis. Of the 17 reported cases of RV sarcoidosis (including ours), 6 patients either died or underwent transplantation before being diagnosed with cardiac sarcoidosis or receiving medical treatment for it.[2,5,9,10]

The lack of accurate methods to detect cardiac sarcoidosis appears to hamper its diagnosis. Sophisticated imaging techniques such as cardiac magnetic resonance (CMR) and PET are not always available, and the data on their diagnostic accuracy are sparse and questionable, especially in regard to early and predominant RV disease. Cardiac magnetic resonance with delayed gadolinium enhancement (DGE)—although a test with relatively high specificity for early sarcoidosis[15,16]—tends to have limited accuracy in differentiating RV sarcoidosis from ARVC in the absence of LV involvement or systemic disease.[17] In the 16 earlier reports (Table I), only 5 of the 9 patients who underwent CMR had DGE results that were suspicious for cardiac sarcoidosis.[6,8,11,12] On the other hand, cardiac PET-FDG seems to be a promising tool to improve disease detection.[18] Diagnostic endomyocardial biopsy, although highly specific for cardiac sarcoidosis, is invasive and carries a relatively high procedural risk. In addition, it has poor sensitivity because of the patchy myocardial involvement in cardiac sarcoidosis.[19] Accordingly, the role of endomyocardial biopsy remains unclear in nonischemic cardiomyopathies, especially when a potentially reversible disease process is clinically suspected.[20-22]

Because of our patient's pacemaker, she could not undergo CMR. An endomyocardial biopsy was unlikely to have changed management and was therefore deferred. Although corticosteroids have improved or halted disease progression in patients with cardiac sarcoidosis,[23] it is unclear whether empiric medical therapy so late in the course of our patient's disease would have changed the primary outcome (transplantation). Last, given the pathologic similarities between cardiac sarcoidosis and giant cell myocarditis, we strongly considered the latter diagnosis. However, in addition to our patient's chronic, indolent clinical course and rather nonfulminant presentation, several pathologic features[24] indicated the diagnosis of sarcoidosis: 1) the well-formed granulomata without individual giant cells, 2) the intensity of the inflammation, 3) the lack of ongoing myonecrosis, and 4) the lack of eosinophils in the infiltrate.

In conclusion, we emphasize that, although RV sarcoidosis most often presents with right-sided ventricular arrhythmias, it can also present with progressive RV failure (in the absence of LV involvement) that most often mimics ARVC. The inability of the currently available invasive and noninvasive tests to accurately detect cardiac sarcoidosis can often lead clinicians into a false diagnosis of ARVC, which can delay life-saving treatment. Accordingly, empiric treatment for cardiac sarcoidosis to evaluate response might prove to be useful in certain patients with predominant RV failure, even though these patients meet the diagnostic criteria for ARVC. Perhaps further advances in imaging techniques will obviate the need for endomyocardial biopsy, lead to early and accurate diagnosis, and improve patient outcomes. We think that cardiac sarcoidosis, distinct from ARVC, should be routinely considered as a cause of severe, unexplained RV failure, and that it is time to update our differential diagnostic criteria.

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