

## Giant Cell Myocarditis and Arrhythmogenic Right Ventricular Dysplasia

### To the Editor:

Right ventricular arrhythmogenic dysplasia (RVAD) is an uncommon entity characterized by ventricular arrhythmia, heart failure, and sudden death in young individuals.<sup>1</sup> Hereditary variants with an autosomal dominant pattern and other mechanisms involved in its etiopathogenesis such as apoptosis and inflammatory processes have been identified, and abnormalities in various genetic loci and intercellular junctional proteins such as plakoglobin and desmoplakin have been described.<sup>2</sup> The presence of focal myocarditis is common in the histopathological study of this cardiomyopathy, but the interpretation of this finding is controversial.<sup>3</sup> This finding has been explained as myocarditis in which fibroadipose repair is based on structural alteration of the right ventricle (RV), or as a sporadic process that develops because of the greater susceptibility of the dysplastic myocardium in these patients.<sup>4</sup>

Giant cell myocarditis is a specific autoimmune disease characterized by acute, refractory, often fulminant heart failure, although chronic variants such as idiopathic dilated cardiomyopathy have been described in retrospective studies.<sup>5</sup> Although it may respond to combined immunosuppressive therapy, heart transplantation (HT) is often necessary.<sup>6</sup> The possibility of recurrence of the disease in a high percentage of patients after HT has been described as characteristic.<sup>6</sup>

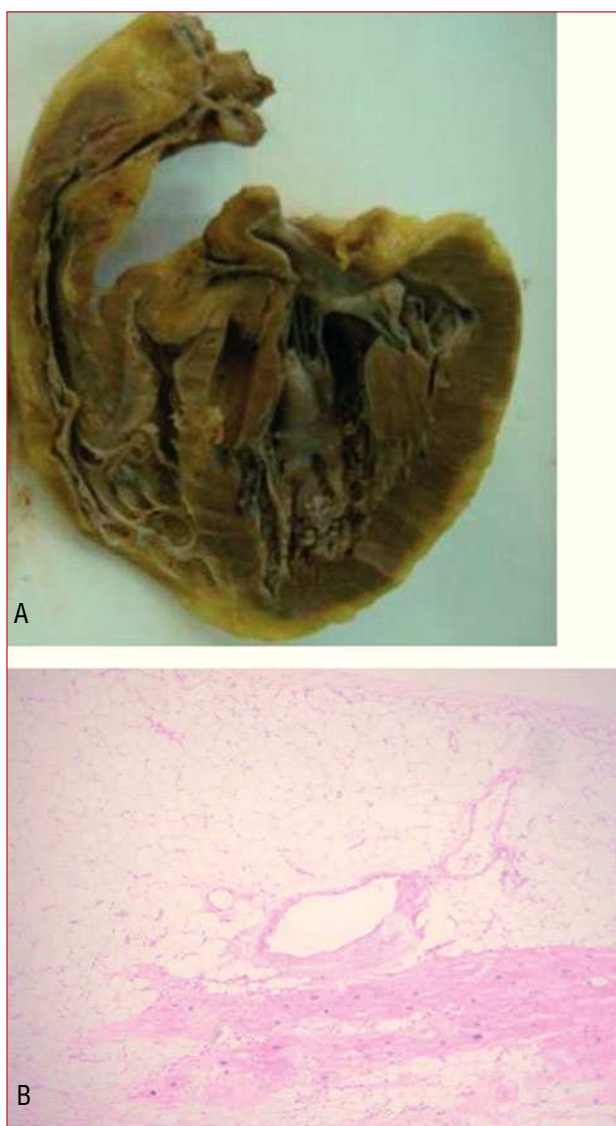
We describe a 38-year-old woman with no family history of heart disease or sudden death, diagnosed 5 years earlier with a cardiomyopathy involving only the RV, with no ventricular arrhythmia observed during the course of the disease. A year earlier, she had been admitted for acute pulmonary edema, at which time she was diagnosed with precirrhosis of the liver due to stasis, with the development of incipient esophageal varices.

The patient was referred to the HT unit and found to be New York Heart Association (NYHA) Class III-IV. The electrocardiogram showed atrial flutter and right bundle-branch block with no epsilon wave. Cardiac magnetic resonance revealed cardiomyopathy with a dilated RV with areas of aneurysms and dyskinesia, particularly in the apex, and moderate-to-severe systolic dysfunction of the left ventricle. Based on the patient's advanced clinical condition, HT was performed.

On pathological study of the explanted heart, the RV showed a thinned wall with aneurysmal dilatations and adipose infiltration over 70% of its thickness (Figure 1, A and B). Microscopy disclosed foci of interstitial lymphocytic myocarditis with giant cells in the interventricular septum (Figure 2A).

Endomyocardial biopsy 2 months after transplantation showed asymptomatic recurrence of the lymphocytic infiltrate and the presence of giant cells (Figure 2B), which improved following adjustment in the immunosuppressive therapy.

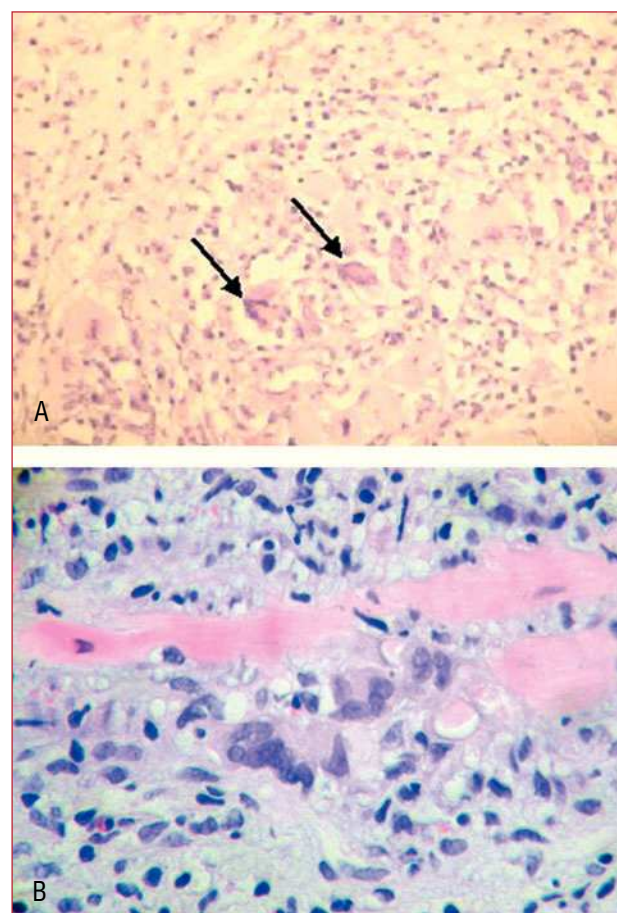
A high percentage of myocarditis with RV involvement alone has been observed in biopsies of patients with no family history and a diagnosis of RVAD based on clinical and imaging evidence; these patients have a more favorable prognosis.<sup>3</sup> Post-transplantation recurrence of myocarditis characterized



**Figure 1.** A: macroscopic image of the right ventricle of the explanted heart showing characteristic thinning and aneurysmal formations of right ventricular arrhythmogenic dysplasia. B: right ventricular wall with predominance of fibroadipose tissue over the muscle fibers.

by giant cells and initial improvement with increased immunosuppression is characteristic of this condition; the medium-term to long-term prognosis is inconclusive.<sup>5,6</sup>

We believe that this case highlights the usefulness of endomyocardial biopsy in cardiomyopathies where RVAD is suspected in the magnetic resonance imaging study, both to identify the characteristic findings and to rule out other entities such as myocarditis with isolated RV involvement. Patchy myocardial involvement is the main limitation of this technique. If a prior histological diagnosis by endomyocardial biopsy had been made in the patient described, empirical immunosuppressive therapy could have been attempted. Because the condition was found after HT, closer follow-up is necessary, given the high probability of recurrence.



**Figure 2.** A: lymphocytic infiltrates and giant cells (arrows) in the septal myocardium of the explanted heart (HE,  $\times 200$ ). B: detailed view of inflammatory infiltrate in a post-transplant biopsy. In the center, 3 multinucleated giant cells and a myocyte are evident (HE,  $\times 400$ ).

Jaime Agüero,<sup>a</sup> Luis Martínez-Dolz,<sup>a</sup>  
Luis Almenar,<sup>a</sup> and Melitina Chirivella<sup>b</sup>

<sup>a</sup>Servicio de Cardiología, Hospital Universitario La Fe, Valencia, Spain

<sup>b</sup>Servicio de Anatomía Patológica, Hospital Universitario La Fe, Valencia, Spain

## REFERENCES

1. Calkins H. Arrhythmogenic right-ventricular dysplasia/cardiomyopathy. *Curr Opin Cardiol.* 2006;21:55-63.
2. Tomé MT, García-Pinilla JM, McKenna WJ. Actualización en miocardiopatía arritmogénica del ventrículo derecho: genética, diagnóstico, características clínicas y estratificación de riesgo. *Rev Esp Cardiol.* 2004;57:757-67.
3. Chimenti C, Pieroni M, Maseri A, Frustaci A. Histologic findings in patients with clinical and instrumental diagnosis of sporadic arrhythmogenic right ventricular dysplasia. *J Am Coll Cardiol.* 2004;43:2305-13.
4. Fontaine G, Fontaliran F, Lascault G, Frank R, Tonet J, Chomette G, et al. Congenital and acquired right ventricular dysplasia. *Arch Mal Coeur Vaiss.* 1990;83:915-20.

5. Davies RA, Veinot JP, Smith S, Struthers C, Hendry P, Masters R. Giant cell myocarditis: clinical presentation, bridge to transplantation with mechanical circulatory support, and long-term outcome. *J Heart Lung Transplant*. 2002;21:674-9.
6. Cooper LT Jr, Berry GJ, Shabetai R. Idiopathic giant-cell myocarditis: natural history and treatment. Multicenter Giant Cell Myocarditis Study Group Investigators. *N Engl J Med*. 1997;336: 1860-6.

much different from those presented now. The high risk of recurrence in patients who have experienced resuscitated sudden death or sustained ventricular tachycardia is well recognized. There is agreement about the need to use an implantable cardioverter defibrillator for secondary prevention,<sup>3</sup> but greater controversy about indicating a defibrillator for primary prevention, because it is not clear how many risk factors are needed for the indication.<sup>4</sup> Even at institutions with specialized units for this condition, the percentage of patients who receive a defibrillator for prevention varies considerably and depends not only on differences in the criteria for indicating the implant, but also on the type of population being cared for.<sup>1,5,6</sup>

The possible discrepancies between the series of Manovel-Sánchez et al<sup>1</sup> and ours may lie in the different proportion of patients in the primary and secondary prevention groups. Additionally, both series may have had patient selection bias, making comparison between them difficult. It is particularly difficult to draw conclusions about the usefulness of risk stratification when analyzing patients with a defibrillator implant as secondary prevention. Because these patients often do not undergo a complete risk assessment, which is not essential when deciding on whether a defibrillator is indicated, they may paradoxically have fewer risk factors than primary prevention patients, despite having more appropriate shocks.

Therefore, there are still many questions in terms of stratifying the risk of our patients and indicating whether a defibrillator is needed for primary prevention: How many risk factors are required? Do all factors have equal weight? How do risk factors work in older patients? How important are other factors that may have an impact, such as ischemic heart disease or atrial fibrillation? What role will genetics play? What will be the role of new imaging techniques such as magnetic resonance and tissue Doppler?

We share the belief that multicenter studies should be conducted. From the Hypertrophic Cardiomyopathy Working Group of the Sociedad Española de Cardiología (Spanish Society of Cardiology), we would like to encourage the development of an ambitious national registry of patients with this condition that covers various related diagnostic and therapeutic aspects. Because of its importance, a registry of

patients with an implanted defibrillator is the section being developed first.

Francisco Marín,<sup>a</sup> Juan R. Gimeno,<sup>b</sup> Juan G. Martínez,<sup>a</sup> and Lorenzo Monserrat<sup>c</sup>

<sup>a</sup>Servicio de Cardiología, Hospital General de Alicante, Alicante, Spain

<sup>b</sup>Servicio de Cardiología, Hospital Virgen de la Arrixaca, Murcia, Spain

<sup>c</sup>Servicio de Cardiología, Hospital Juan Canalejo, La Coruña, Spain

Lorenzo Monserrat is receiving research aid funds from the Aventura Foundation. Lorenzo Monserrat is funded by the Red Cardiovascular (Cardiovascular Network, RECAVA) of the Instituto de Salud Carlos III (C03/01).

## REFERENCES

1. Marín F, Gimeno JR, Payá E, García-Alberola A, Pérez-Álvarez L, Fernández X, et al. Desfibrilador automático implantable en la miocardiopatía hipertrófica. Experiencia de 3 centros. *Rev Esp Cardiol.* 2006;59:537-44.
2. Manovel-Sánchez AJ, Pedrote-Martínez A, Arana-Rueda E, Errazquin-Sáez de Tejada F. Miocardiopatía hipertrófica y desfibrilador automático implantable. *Rev Esp Cardiol.* 2007;60:784.
3. Elliott PM, Sharma S, Varnava A, Poloniecki J, Rowland E, McKenna WJ. Survival after cardiac arrest or sustained ventricular tachycardia in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 1999;33:1596-601.
4. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, et al. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *Eur Heart J.* 2003;24:1965-91.
5. Maron BJ, Estes M, Maron MS, Almquist AK, Link MS, Udelson JE. Primary prevention of sudden death as a novel treatment strategy in hypertrophic cardiomyopathy. *Circulation.* 2003;107:2872-5.
6. Elliott PM, Gimeno JR, Tomé MT, Shah J, Ward D, Thaman R, et al. Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy. *Eur Heart J.* 2006;27:1933-41.