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REVIEW TOPIC OF THE WEEK

Cardiac Sarcoidosis

David H. Birnie, MD, MBChB,[a] Pablo B. Nery, MD,[a] Andrew C. Ha, MD,[b] Rob S.B. Beanlands, MD[a]

ABSTRACT

Clinically manifest cardiac involvement occurs in perhaps 5% of patients with sarcoidosis. The 3 principal manifestations of cardiac sarcoidosis (CS) are conduction abnormalities, ventricular arrhythmias, and heart failure. An estimated 20% to 25% of patients with pulmonary/systemic sarcoidosis have asymptomatic cardiac involvement (clinically silent disease). In 2014, the first international guideline for the diagnosis and management of CS was published. In patients with clinically manifest CS, the extent of left ventricular dysfunction seems to be the most important predictor of prognosis. There is controversy in published reports as to the outcome of patients with clinically silent CS. Despite a paucity of data, immunosuppression therapy (primarily with corticosteroids) has been advocated for the treatment of clinically manifest CS. Device therapy, primarily with implantable cardioverter-defibrillators, is often recommended for patients with clinically manifest disease. (J Am Coll Cardiol 2016;68:411–21) © 2016 by the American College of Cardiology Foundation.

Sarcoidosis is a multisystem, granulomatous disease of unknown etiology. Accumulating evidence suggests that it is caused by an immunological response to an unidentified antigenic trigger in genetically susceptible persons (1). Noncaseating granulomas are the histopathological hallmark (**Figure 1**). The lungs are affected in more than 90% of patients, and the disease can also involve the heart, liver, spleen, skin, eyes, parotid gland, or other organs and tissues. Most disease (70%) occurs in patients 25 to 60 years of age (2,3), and it is rare in people <15 or >70 years of age (4). Sarcoidosis is a worldwide disease, with a prevalence of about 4.7 to 64 in 100,000; the highest rates are reported in northern Europeans and African Americans, particularly in women (2,3).

Familial clustering indicates a strong genetic element in sarcoidosis (5). Gene linkage studies suggest that genes influencing clinical presentation of sarcoidosis are likely to be different from those that underlie disease susceptibility (6). Associations have been described with HLA DQB*0601 (7) and the tumor necrosis factor allele TNFA2 (8) in Japanese patients with cardiac sarcoidosis (CS). Much remains to be learned about genetic/environmental interactions in sarcoidosis in general and in relation to disease phenotypes (e.g., organ predilection).

Clinically manifest cardiac involvement occurs in perhaps 5% of patients with sarcoidosis. In addition, many patients with pulmonary/systemic sarcoidosis have asymptomatic cardiac involvement (clinically silent disease). This finding was initially on the basis of autopsy studies, which estimated the prevalence of cardiac involvement to be at least 25% of patients with sarcoidosis (9,10). These autopsy findings are consistent with recent data using late gadolinium enhanced (LGE) cardiovascular magnetic resonance (CMR) technology (**Table 1**).

Studies suggest that CS seems to be becoming more prevalent. However, this is likely due to improvements in imaging and/or more thorough investigation, rather than a true increase in prevalence. In Finland, the rate of diagnosis of CS increased more than 20-fold between 1988 and 2012 (11). In the United States, the incidence of patients who underwent transplantation and had CS as the

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From the [a]Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada; and the [b]Peter Munk Cardiac Centre, University Health Network and Department of Medicine, University of Toronto, Toronto, Ontario, Canada. Dr. Beanlands has served as a consultant for Lantheus Medical Imaging and Jubilant DRAXImage; and has received research grants from GE Healthcare, Lantheus Medical Imaging, and Jubilant DRAXImage. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

AV = atrioventricular

CMR = cardiac magnetic resonance

CS = cardiac sarcoidosis

ECG = electrocardiogram

FDG = fluorodeoxyglucose

ICD = implantable cardioverter-defibrillator

LGE = late gadolinium enhancement

LV = left ventricular

PET = positron emission tomography

VT = ventricular tachycardia

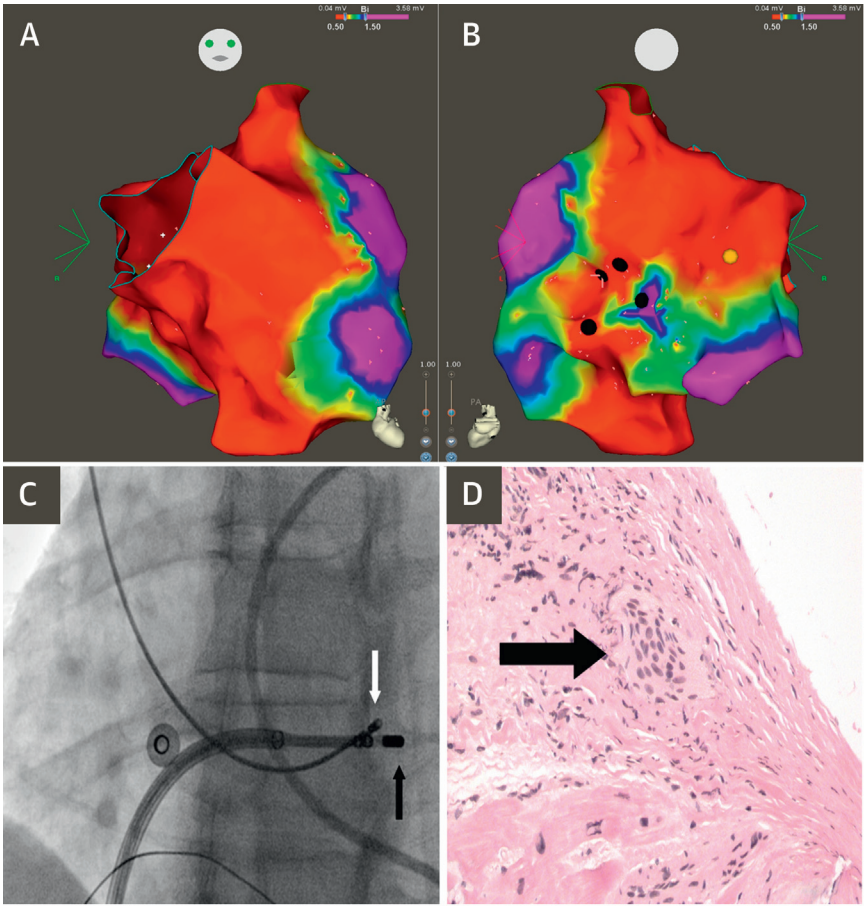
etiology of cardiomyopathy increased from 0.1% (1994 to 1997) to 0.5% (2010 to 2014) (12).

There is a growing realization that CS can be the first manifestation of sarcoidosis in any organ. Between 16% and 35% of patients presenting with complete atrioventricular (AV) block (age <60 years) (13,14) or ventricular tachycardia (VT) of unknown etiology (15,16) have previously undiagnosed CS as the underlying etiology. Also, CS as the underlying cause of heart failure is often missed; for example, core left ventricular (LV) biopsies at the time of LV assist device implantation found previously undiagnosed CS in 6 of 177 patients (3.4%) (17). Roberts et al. (18) examined explanted hearts, and 10 of 346 (3%) had undiagnosed CS. Also, CS can present with features similar to arrhythmogenic right ventricular (RV) cardiomyopathy (19).

CLINICAL MANIFESTATIONS

Clinical features of CS depend on the location, extent, and activity of the disease. The principal manifestations are conduction abnormalities; ventricular arrhythmias, including sudden death; and heart failure. These patients are usually highly symptomatic, with the symptom complex dependent on presentation. Furthermore, cardiac symptoms usually dominate over extracardiac symptoms, as patients generally only have low-grade pulmonary and no other organ involvement (14,15,20,21). Indeed, most patients with clinically manifest CS

FIGURE 1 Electroanatomic Bipolar Voltage Map of the Right Ventricle



(A) Anterior and **(B)** posterior views. **Green, yellow**, and **red** indicate low-voltage regions; **purple** denotes regions of normal voltage, defined as ≥1.5 mV. **Black circles** illustrate areas targeted for biopsy. **Yellow circle** illustrates location of right bundle. **(C)** Fluoroscopy images obtained in the left anterior oblique 25° projection showing bioptome **(white arrow)** targeting the low-voltage region in the right ventricular septum, adjacent to mapping catheter **(black arrow)**. **(D)** Microscopic view of an endomyocardial biopsy specimen obtained from the right ventricular septum showing noncaseating granuloma **(arrow)**. Hematoxylin-eosin; magnification ×200. Reproduced with permission from Nery et al. (30).