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Insights into biopsy-proven cardiac sarcoidosis in patients with heart failure

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Sarcoidosis is a multisystem inflammatory disease of unknown etiology that is characterized histologically by the presence of non-caseating granulomas. It most commonly affects the lungs and thoracic lymph nodes; however, autopsy studies have shown that up to 27% of patients with sarcoidosis have cardiac involvement.[1] The diagnosis of cardiac sarcoidosis (CS) is challenging, because specimens from an endomyocardial biopsy (the gold standard) are confirmatory in only 32% of patients.[2] Patients diagnosed with CS who present with heart failure symptoms have a worse prognosis than those who present with other symptoms[3] and have acceptable long-term outcomes without recurrence after heart transplantation.[4]

The Heart Rhythm Society (HRS) recommends that patients with extracardiac sarcoidosis proven by biopsy specimen undergo advanced cardiac imaging if they have an abnormal electrocardiogram (ECG), abnormal echocardiogram, or symptoms (palpitations, syncope, or presyncope).[5] We sought to determine how well this recommendation performed if applied to our population of patients with CS proven by biopsy specimen who initially presented with heart failure.

A retrospective analysis was performed of 27 consecutive patients at the Cleveland Clinic with CS proven by myocardial biopsy specimen from 2002 to 2014. Patients were included with New York Heart Association Functional Classification ≥ II symptoms and a left ventricular ejection fraction of ≤50%. Baseline data were obtained on all patients before cardiac tissue diagnosis, including clinical characteristics, echocardiographic, ECG, and laboratory findings. Positron emission tomography with 18F-fluoro-2-deoxy-D-glucose (FDG-PET) and cardiac magnetic resonance imaging (CMR) were evaluated when available (Table).

Patients were on average in their sixth decade of life and more likely to be Caucasian and male. The ECGs in all patients showed abnormalities, as defined by a complete right or left bundle branch block, axis deviation, ventricular tachycardia, frequent premature ventricular contractions, or abnormal Q waves. Eighteen patients (67%) had class III or IV heart failure

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symptoms, 16 (59%) had ventricular tachycardia, and 15 (56%) had advanced heart block requiring pacing. All patients met at least 1 criterion needed to warrant further investigation with FDG-PET or CMR based on the HRS consensus statement.[5] In contrast, only 8 of 27 patients (30%) met Japanese Ministry of Health and Welfare criteria for CS before cardiac biopsy. Of the 16 patients who underwent FDG-PET, 12 had matching segmental defects in perfusion and FDG and 12 had segments with reduced perfusion and enhanced FDG uptake ("mismatched segments"). All patients had matching or mismatched defects. In addition, the 10 patients who underwent contrast-enhanced CMR had late gadolinium enhancement in a pattern consistent with CS. Fourteen patients (52%) had isolated CS, defined as lack of extracardiac symptoms, diagnostic biopsy specimen, or imaging findings, including CMR and FDG-PET.

There were 19 heart transplantations and 5 left ventricular assist devices (LVADs) in the cohort. Of the 5 patients with LVADs, all of whom went on to heart transplantation, 2 had apical core biopsy specimens that were nondiagnostic but were later confirmed to be sarcoidosis after analysis of the explanted heart. Eight of the 19 patients receiving heart transplantation or LVAD (42%) were previously unaware of a diagnosis of systemic or CS until the time of pathologic confirmation. Ten of the 19 heart transplant patients had isolated CS.

All patients were maintained on low-dose prednisone after transplantation. There was no recurrence of CS on endomyocardial biopsy specimens in any of the patients after 25,993 total patient follow-up days with an average follow-up of 4.2 years per patient.

This analysis highlights several important points regarding CS proven on biopsy specimen in patients presenting with cardiomyopathy. The LVAD apical core was positive in only 3 of the 5 patients who later went on to heart transplantation, highlighting the heterogeneous involvement of sarcoid granulomas in the myocardium as well as the difficulty in obtaining a positive biopsy sample, even in patients with severe cardiomyopathy. Isolated CS was present in 52% of the patients, validating the high prevalence seen in other studies of biopsy specimen–proven CS.[3,4] However, this prevalence may be influenced by selection bias, because patients with extracardiac biopsy specimen–proven sarcoidosis are more likely to have a non-invasive evaluation of cardiac involvement. All patients had an abnormal ECG, reduced LVEF, and findings consistent with the diagnosis of CS on multimodality imaging, including CMR and FDG-PET. This corroborates the findings of the recently published HRS consensus statement on the diagnosis of CS in patients presenting with arrhythmias or heart block and suggests that patients with a cardiomyopathy severe enough to have a positive endomyocardial biopsy specimen or warrant advanced heart failure therapies will have findings consistent with the diagnosis on FDG-PET or CMR.[5] Given the difficulty in sampling an affected area for a histologic diagnosis, we agree with the HRS guidelines that a non-invasive approach with CMR or PET imaging is favored.

Currently, no consensus recommendations exist regarding the diagnosis and screening of CS in patients presenting with non-ischemic cardiomyopathy. Our results add to the small but growing body of literature in this field.

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Table

Clinical Characteristics and Japanese Ministry of Health and Welfare Criteria in Patients with Biopsy Specimen– Proven Cardiac Sarcoidosis and Cardiomyopathy

Variable	Mean ± SD or No. (%)
	(N = 27)
Age, y	53.8 ± 9.5
Male	16 (59)
Caucasian	21 (78)
NYHA Functional Classification III–IV	18 (67)
Hypertension	15 (56)
Hyperlipidemia	12 (44)
Smoking	5 (19)
Obese	5 (19)
Diabetes	6 (22)
Coronary artery disease (CABG or PCI)	5 (19)
Atrial fibrillation	10 (37)
Anemia	8 (30)
Implantable cardioverter defibrillator	23 (85)
Ventricular tachycardia	16 (59)
Heart transplantation	19 (70)
Left ventricular assist device	5 (9)
eGFR, ml/min/1.73 m^2	75 ± 22
Ejection fraction, %	27 ± 11
Electrocardiogram findings	
QRS duration, msec	135 ± 30
Left bundle branch block or IVCD	3 (11)
Right bundle branch block	7 (26)
JMHW major criteria	
Extracardiac involvement	13 (48)
Advanced atrioventricular block	15 (56)
Depressed left ventricular ejection fraction	27 (100)
Basal septal thinning	4 (15)
JMHW minor criteria	
Abnormal electrocardiogram findings	27 (100)
Nuclear imaging perfusion defect (n = 16)	16 (100)
Gadolinium-enhanced CMR (n = 12)	12 (100)

CABG, coronary artery bypass graft; CMR, cardiac magnetic resonance imaging; eGFR, estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration formula; IVCD, intraventricular conduction defects; JMHW, Japanese Ministry of Health and Welfare; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.