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EDITORIAL COMMENT

Detection of Cardiac Sarcoidosis

A Balancing Act Between Symptoms and Imaging Findings*

Amit R. Patel, MD

Sarcoidosis is a rare granulomatous disorder that is associated with myocardial damage in approximately 20% of individuals, yet the cardiac involvement is only rarely evident clinically. The mechanism of myocardial damage could be a direct result of active inflammation or due to the development of myocardial scar as the inflammation heals. Myocardial damage might also occur secondary to side effects of corticosteroid treatment itself or due to potentially unrelated processes such as myocardial infarction.

Regardless of the exact nature of the myocardial damage that occurs in patients with sarcoidosis, it is believed to be associated with a significantly increased risk of death and life-threatening arrhythmias (1) even in the absence of overt signs of cardiac involvement such as the presence of symptoms or a reduction in left ventricular ejection fraction (2). Unfortunately, because cardiac sarcoidosis is a patchy disorder that often involves only small amounts of the myocardium, commonly used cardiac tests such as the electrocardiogram (ECG), echocardiogram (echo), myocardial perfusion imaging, and even endomyocardial biopsy have a poor diagnostic sensitivity (3). Cardiac magnetic resonance (CMR), because of its ability to accurately identify even small areas of myocardial damage based on the presence of late gadolinium enhancement (LGE), can readily identify individuals with cardiac sarcoidosis or its associated myocardial damage (4). Recent studies have also suggested that cardiac F(18)-fluorodeoxyglucose positron emission tomography (PET) may be similarly useful (5). Cardiac PET may have the additional value of being an imaging-based biomarker of inflammation that can be observed to assess for treatment response (6).

The Heart Rhythm Society recently published an expert consensus document in which CMR and PET play a central role in the diagnosis and management of patients with suspected cardiac sarcoidosis (7). According to this document, it is suggested that all patients with sarcoidosis should be screened with a history, ECG, and echo. Those with a significant abnormality on any of these examinations should be referred for CMR or PET to further evaluate for cardiac involvement and to help identify those at highest risk for sudden cardiac death.

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In this issue of *iJACC*, Kouranos et al. (8) present data from a cohort of 321 patients with biopsy-proven extracardiac sarcoidosis who underwent a comprehensive screening program that included history, ECG, echo, event monitoring, and CMR to evaluate for cardiac involvement. This study represents the largest cohort published to date with regard to the evaluation of possible cardiac sarcoidosis. Thirty percent of patients in this cohort were diagnosed with cardiac sarcoidosis according to Heart Rhythm Society criteria. Ninety-seven percent of these patients were identified by the presence of LGE on CMR. The high diagnostic performance of CMR in this setting, however, is not surprising because the Heart Rhythm Society criteria include the presence of LGE as evidence of cardiac sarcoidosis. Similar to previously described cohorts, the presence of cardiac symptoms, ECG, event monitoring, and echo each independently had a poor sensitivity for the detection of cardiac sarcoidosis. When these tests were combined, the sensitivity for detecting cardiac sarcoidosis increased significantly but at the expense of a substantial decrease in diagnostic specificity.

The cohort was followed up for a median of 7 years, and 7.2% of individuals reached a composite endpoint that included death, life-threatening arrhythmias,

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From the Cardiac Imaging Center, Departments of Medicine and Radiology, University of Chicago Medicine, Chicago, Illinois. Dr. Patel is supported by research grants from Astellas Pharma, Philips Healthcare, and Myocardial Solutions.

unplanned hospitalization for heart failure, and cardiac transplantation (8). The presence of LGE was an independent predictor of the composite endpoint. When nonsustained ventricular tachycardia was also included as part of the composite endpoint, the hazard ratio was 5.68. In fact, those with LGE had a >25% event rate during the follow-up period that translates into an annualized rate of nearly 4% per year. Although these findings convincingly illustrate (similar to several previous studies) the utility of CMR for risk-stratifying patients with suspected cardiac sarcoidosis, the strength of the current data is somewhat limited by the fact that 9 subjects lost to follow-up had to be excluded from analysis. It must also be noted that all patients included in the cohort were white, and it is unknown if the findings from the current study would be applicable to other ethnicities.

The clinical utility of LGE imaging is well established in a variety of clinical scenarios; however, it is worrisome that in this study (8) in which CMR was performed at experienced centers, the interobserver agreement for identifying LGE for the purpose of detecting cardiac sarcoidosis was somewhat limited, with a κ of 0.78. If CMR is going to be used as a screening test for the detection of cardiac sarcoidosis, the development of analysis tools to help improve the interobserver agreement for the detection and quantification of LGE will be needed. Furthermore, the relatively high cost and lack of availability of CMR at most hospital centers may make it less well suited to serve as a screening test. Although the current study and several others strongly suggest that a "standard" echo may not be a particularly helpful test in the evaluation of and screening for cardiac sarcoidosis, newer echo approaches such as measuring global longitudinal strain may accurately identify patients with sarcoidosis who have LGE (9). Perhaps the ideal screening tool would be the use of a yet-to-be-discovered serum biomarker.

A particular strength of this study is that Kouranos et al. (8) attempt to place the imaging findings into the context of patient symptoms and ECG abnormalities. In fact, they convincingly show that CMR is a particularly useful tool in patients with sarcoidosis who have either an ECG abnormality or symptoms such as chest pain, palpitations, pre-syncope, syncope, or heart failure. In these patients, the presence of LGE was a powerful predictor of significant cardiac events. Conversely, although LGE could be found in asymptomatic patients who had no significant symptoms or ECG abnormalities, its presence was not an independent predictor of adverse events. It is unclear if these individuals were at risk for other cardiovascular complications such as the development of left ventricular dysfunction, atrial arrhythmias, or cardiac symptoms. The current data suggest that the proposed Heart Rhythm Society strategy of screening patients with sarcoidosis who have a history and ECG followed by advanced imaging only in those with an abnormality would adequately differentiate those patients who are at risk for death, life-threatening arrhythmias, unplanned hospitalization for heart failure, or cardiac transplantation. However, such a strategy may not identify lower risk patients who have myocardial damage in the absence of symptoms or ECG that could potentially still derive other benefits from medical therapy. Importantly, the current data also suggest that the Heart Rhythm Society recommendation to screen all patients with "standard" echo might not be as helpful as we would hope, in the absence of advanced measurements such as global longitudinal strain.

Although this study (8) adds significantly to the existing data regarding the role of CMR for the detection of cardiac sarcoidosis and provides important insights into potential cardiac screening strategies for patients with sarcoidosis, several important questions remain: How often should patients with sarcoidosis undergo screening for cardiac involvement? Which patients with LGE should receive an implantable cardioverter-defibrillator? Who should be treated with immunosuppressive therapy and for what duration? How should patients with cardiac sarcoidosis be monitored for treatment response? While we await the answers to these questions, the current literature seems to suggest that the use of CMR as a first-line imaging test for the detection of myocardial damage in patients with sarcoidosis may be reasonable if performed at an experienced CMR center.

ADDRESS FOR CORRESPONDENCE: Dr. Amit R. Patel, Departments of Medicine and Radiology, University of Chicago, 5758 South Maryland Avenue, MC 9067, Chicago, Illinois 60637. E-mail: amitpatel@uchicago.edu.

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