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Cardiac Sarcoidosis: Oldies but Not Goodies

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Cardiac involvement in sarcoidosis is being increasingly noted since it has been recognized in the early 20th century and is associated with poor prognosis. Cardiac sarcoidosis is rare but is potentially fatal with a wide spectrum of clinical manifestations ranging from an incidentally discovered, benign condition to fatal cardiomyopathy, arrhythmias, and even sudden cardiac death.[1)2)] Cardiac involvement may occur at any point during the course of sarcoidosis, may occur in the absence of pulmonary or systemic involvement, and may be a presenting feature.[1-3)] Arrhythmias or conduction defects are the most common cardiac manifestations reflecting granulomatous infiltration within the conduction system or ventricular walls and are the most common causes of death due to cardiac sarcoidosis; however, progressive heart failure due to massive granulomatous infiltration of the myocardium accounts for at least 25% of deaths.[1)3)4)] Sarcoidosis can involve any part of the heart, including myocardium, endocardium, and pericardium.[3)4)] The areas of involvement in descending order of frequency are the left ventricular free wall, ventricular septum, papillary muscles, right ventricle, and atria.[3)] Obliteration of the sinoatrial node, atrioventricular node, or the bundle of his may occur.[4)] Valvular dysfunction may result from localized involvement of the papillary muscles causing significant valvular insufficiency in rare cases.[4)]

Diagnostic Challenge of Cardiac Sarcoidosis

Cardiac involvement in sarcoidosis has been extremely difficult to diagnose clinically because the clinical manifestations are non-specific, and the sensitivity and specificity of diagnostic modalities are limited. A resting electrocardiogram (ECG) is an appropriate screening test to order in all patients with confirmed or suspected sarcoidosis. Abnormalities on ECG including conduction disturbances, arrhythmias, or nonspecific ST and T-wave changes can be demonstrated in up to one-third of sarcoid patients.[5)] However, ECG remains a poorly sensitive test since the significance of these alterations and their relation to cardiac lesions and the patients' symptoms are often unclear. Twenty-four-hour Holter monitoring and exercise ECGs can detect abnormalities even when resting ECGs are normal. Technetium-99m scintigraphy is more sensitive than thallium-201 scintigraphy. Both modalities exhibit the "reverse distribution" phenomenon (i.e., the focal defects detected in the resting phase of thallium scanning disappear or decrease in size during thallium stress imaging or after dipyridamole infusion). These results are quite different from those observed in patients with coronary artery disease, in which defects are unchanged or enhanced after exercise or intravenous dipyridamole. Gallium-67 heart uptake predicts a better response to corticosteroid treatment. Contrast-enhanced magnetic resonance imaging and 18F-fluorodeoxyglucose positron emission tomography are most sensitive, and the findings seem to correlate with disease activity (Table 1).[2)6)] An endomyocardial biopsy is preferable, but the procedure has a sensitivity as low as 20%.[1)]

Thus the search for a reliable, reproducible, and easily available diagnostic tool for cardiac sarcoidosis continues. A recent updated guideline was established in 2006 by the Japanese Ministry of Health and Welfare since it was first published in 1993 (Table 2).[6)7)]

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Table 1. Multimodality imaging for diagnosis of cardiac sarcoidosis[2)]

Diagnostic test	Feature	Sensitivity	Specificity
Electrocardiogram	Conduction disturbances, arrhythmias	Low	Low
Echocardiography	Abnormal wall motion, regional wall thinning/thickening, depressed ejection fraction, pericardial effusion	Low to moderate	Low
^{201}Thallium scintigraphy	Segmental perfusion defect	Moderate	Moderate
^{67}Gallium scintigraphy	Increased myocardial uptake	Low	High
^{18}F FDG-PET	Increased myocardial uptake	High	Moderate to high
CMR	High intensity lesions, thinning of ventricular wall	Moderate to high	High

FDG-PET: fluorodeoxyglucose positron emission tomography, CMR: cardiac magnetic resonance

Table 2. Updated guideline for diagnosis of cardiac sarcoidosis by the Japanese Ministry of Health and Welfare in 2006[6)]

Histologic diagnosis group

Cardiac sarcoidosis is confirmed when endomyocardial biopsy specimens demonstrate noncaseating epithelioid cell granulomas with histological or clinical diagnosis of extracardiac sarcoidosis.

Clinical diagnosis group

Although endomyocardial biopsy specimens do not demonstrate noncaseating epithelioid cell granulomas, extracardiac sarcoidosis is diagnosed histologically or clinically and satisfies the following conditions and more than one in six basic diagnostic criteria.

1. 2 or more of the 4 major criteria are satisfied.
2. 1 in 4 of the major criteria and 2 or more of the 5 minor criteria are satisfied.

Major criteria

1. Advanced atrioventricular block.
2. Basal thinning of the interventricular septum.
3. Positive ^{67}gallium uptake in the heart.
4. Depressed ejection fraction of the left ventricle (<50%).

Minor criteria

1. Abnormal ECG findings: ventricular arrhythmias (ventricular tachycardia, multifocal or frequent PVCs), CRBBB, axis deviation or abnormal Q-wave.
2. Abnormal echocardiography: regional abnormal wall motion or morphological abnormality (ventricular aneurysm, wall thickening).
3. Nuclear medicine: perfusion defect detected by ^{201}thallium or ^{99m}technetium myocardial scintigraphy.
4. Gadolinium-enhanced CMR imaging: delayed myocardial enhancement.
5. Endomyocardial biopsy: interstitial fibrosis or monocyte infiltration over moderate grade.

CMR: cardiac magnetic resonance, CRBBB: complete right bundle branch block, ECG: electrocardiogram, PVC: premature ventricular contraction

Salient Features on Echocardiography

Echocardiography may be a useful imaging tool for myocardial sarcoidosis. Echocardiographic abnormalities have been reported in patients with cardiac sarcoidosis, but the prevalence, spectrum, and clinical significance of echocardiographic findings are still unknown. Abnormalities seen on transthoracic echocardiography, which include septal thinning, left ventricular regional systolic dysfunction, pericardial effusion, ventricular aneurysms, left ventricular diastolic dysfunction, and valvular abnormalities, are usually seen in advanced disease and can be detected in only 14% of patients with systemic sarcoidosis and cardiac involvement.[8)] Cardiac lesions may also produce an increase in the thickness of the interventricular septum, mimicking hypertrophic cardiomyopathy. This suggests that two dimensional echocardiography may not be sensitive enough to detect mild or small localized abnormalities, which may occur in the early stages of cardiac involvement.

In this issue of the Korean Circulation Journal, Sun et al.[9)] reported that the prevalence of two characteristic echocardiographic findings suggesting cardiac sarcoidosis (basal septal thinning or localized aneurysmal dilatation without coronary artery disease) in patients with pacemaker or implantable cardiac defibrillator (ICD) was very low (1.2% in the pacemaker group and 4.0% in the ICD group, 1.5% in the study subjects). And the prognosis was poor in patients with cardiac sarcoidosis. Considering low yield of endomyocardial biopsy and rare systemic involvement in patients with cardiac sarcoidosis, the authors suggest that echocardiographic findings can be useful in the selected group of patients, as characteristic basal septal thinning or aneurysmal dilatation can be regarded as a supporting evidence of cardiac involvement in sarcoidosis. The most important issue in cardiac sarcoidosis is the diagnostic difficulty and poor prognosis. As the authors have noted, clinical impact of diagnosis of cardiac sarcoido-

sis based on combination of both the clinical features of significant arrhythmias warranting device therapy and the characteristic echocardiographic findings needs to be tested in future investigations.

In conclusion, clinicians should consider the possibility of cardiac sarcoidosis in the evaluation of an otherwise healthy young patient who develops unexplained cardiomyopathy or arrhythmias. Given the grave prognosis of cardiac sarcoidosis, cardiac signs or symptoms in a patient with known sarcoidosis should alert the physician to perform an aggressive workup including ECG screening and multimodality imaging for confirming the diagnosis of cardiac sarcoidosis.

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