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MRI bolsters detection of cardiac sarcoidosis

Delayed enhancement approach offers extra diagnostic information in inconclusive cases

The first description of sarcoidosis dates back to 1869, though the disease was not named until 1899. The first report of cardiac involvement in patients with systemic sarcoidosis came in 1929.[1] The possibility of cardiac involvement was suggested again in 1933, with reference to two autopsy cases.[2] The presence of giant cell granulomas in patients with endocardial fibrosis was described in 1937.[3] In 1952, a separate study reported 20% cardiac involvement in nearly 100 necropsies with systemic sarcoidosis.[4] Most documented instances consisted of combined case reports up until the end of the 20th century.

Systemic sarcoidosis predominantly affects the lung and lymph nodes, though any organ systems can be affected. The disease is seen most often in young adults, with a slightly higher incidence in the Afro-Caribbean population than the Caucasian population (35 cases per 100,000, as opposed to 10 cases per 100,000), though the highest incidence is reported in Scandinavians (50 cases per 100,000).[5] Monozygotic twins and individuals testing positive for human leukocyte antigen-DQB1*0601 are at the greatest risk of developing sarcoidosis.

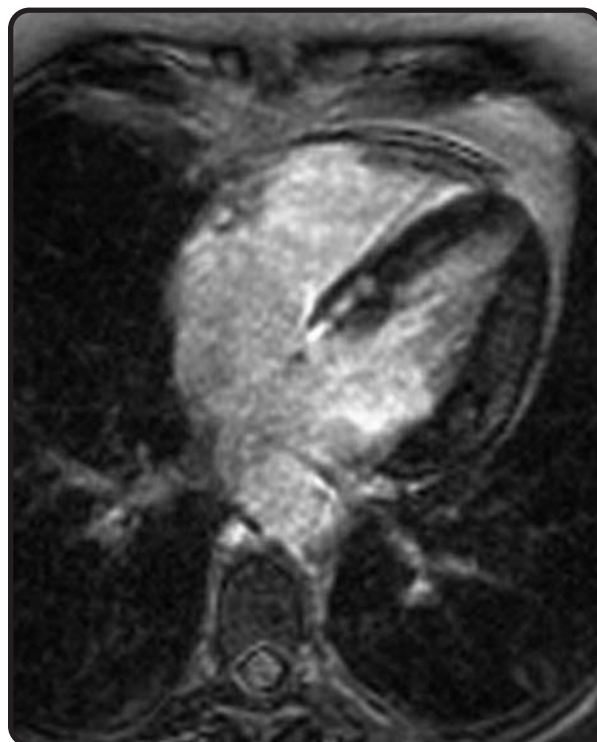Cardiac involvement occurs in around 50% of patients diagnosed with

FIGURE 1. Long-axis four-chamber contrast-enhanced 3D turbo flash sequence (TR 750/TE 4.5/TI 210 msec) reveals multiple areas of delayed enhancement in the myocardium of left and right ventricles.

systemic sarcoidosis.[6,7] Because premortem diagnosis of cardiac sarcoidosis is a complex and challenging procedure, the highest rates of cardiac involvement are reported from postmortem histology.

Retrospective studies describe a wide range of myocardial presentations in postmortem examinations, ranging from 20% to nearly 80%.[6,8]

The etiology of sarcoidosis remains uncertain. Causative factors include infection with *Mycobacterium tuberculosis*, mycoplasma, or corynebacteria. Exposure to aluminum, talcum powder, clay, and pollen can also contribute. These antigens may bind to CD4 T cell receptors, which are then activated.

The activated T cells differentiate in the early stages of disease into type 1 helper effector cells, which produce macrophage-activating interferon-γ and interleukin-2, which leads to local inflammation. Type 2 helper cells are formed in the later stages of disease. These produce IL-10 and transforming growth factor-β, resulting in antiinflammatory effects and tissue scarring.[9] Any part of the heart can be infiltrated with sarcoid granulomas, but the myocardium is the most frequently affected area.

CLINICAL MANIFESTATIONS

Clinical manifestation can range from asymptomatic changes to high-risk ventricular tachyarrhythmias, depending on the extent and location of infiltration.[10] Early-stage infiltration, with localized myocardial lesions, leads to local hypertrophia or dyskinetic wall motions. Later stage infiltration can

cause scarring and remodeling, with the risk of local aneurysms.

A wider, diffuse area of affected tissue can cause global myocardial hypokinesias that may even cause the heart's pumping mechanism to fail. Infiltration of the heart's conducting system may result in first-degree heart block, complete heart block, or a bundle branch block. Infiltration of the ventricular myocardium can cause reentry tachyarrhythmias, the most common clinical manifestation.

Tachyarrhythmia accounts for 67% of all cases of sudden heart death in cardiac sarcoidosis patients.[11] Affected atrial tissue can result in supraventricular arrhythmias, though these are less common. Congestive heart failure is another manifestation of cardiac sarcoidosis, causing death in up to 25% of patients. High-risk tachyarrhythmias occur in only 5% of patients but are associated with a poor prognosis.[12-13]

DIAGNOSTIC TOOLS

Methods of diagnosing cardiac sarcoidosis include electrocardiography, echocardiography, thallium-201 scintigraphy, gallium-67 scintigraphy, PET, MRI, and endomyocardial biopsy.

Electrocardiac abnormalities can be seen in up to 50% of patients with cardiac sarcoidosis, and this method is widely used for diagnosis. The significance of these changes, however, and their correlation to cardiac lesions are vague. A 1994 report of approximately 300 cardiac sarcoidosis cases revealed that 45% of patients had ventricular tachyarrhythmias, 38% had bundle branch block, 28% supraventricular arrhythmias, and 16% sudden heart death.[14]

Pathological echocardiography is noted in 14% to 41% of all patients with cardiac sarcoidosis.[15] Findings include septal thinning or thickening, left ventricular regional dyskinesia,

ventricular aneurysms, systolic and diastolic dysfunctions, valvular abnormalities, and pericardial effusion. Echocardiography may visualize myocardial abnormalities but lacks sensitivity in detecting myocardial involvement. Although myocardial sarcoidosis increases the echogenicity of the myocardium, only large granulomas can usually be seen. Patchy infiltrations remain undetected for the most
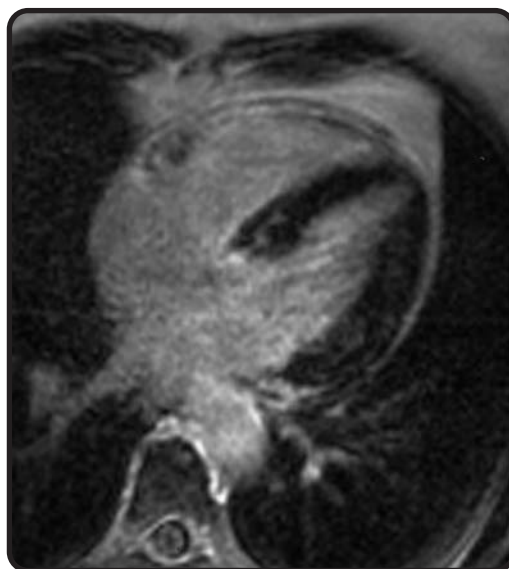

FIGURE 2. Same patient as in Figure 1 after corticosteroid therapy. Long-axis contrast-enhanced 3D turbo flash sequence (TR 750/TE 4.5/TI 210 msec) shows notable decrease in size of sarcoid lesions.

part. Transesophageal echocardiography is not yet established for the diagnosis of cardiac sarcoidosis.

A study highlighting the utility of radionuclide myocardial scanning in patients with cardiac sarcoidosis[16] suggests that myocardial muscle cells show a normal uptake of Tl-201, whereas uptake is lower in areas of scarring, necrosis, or inflammation. These so-called cold spots are primarily unclear and occur in ischemia as well as sarcoidosis.

Differential diagnosis can be made from "reverse distribution," a phenomenon in which cold spots detected in the resting phase decrease or even disappear in the stress phases. This is due

to a local, reversible microvascular constriction in coronary arteries around the sarcoid granulomas. The phenomenon is observed in patients with cardiac sarcoidosis but not in those with ischemia.

SCINTIGRAPHY LIMITATIONS

The importance of Tl-201 scintigraphy is limited. Low spatial resolution and overlaying artifacts on images can reduce the specificity of results.[17] Scintigraphy with Ga-67 provides an alternative option for diagnosing cardiac involvement in active disease. Because uptake is seen in areas of active inflammation, it could be a useful tool for monitoring treatment efficacy.

Areas with known sarcoid infiltration that show Tl-201 uptake but little or no Ga-67 uptake may indicate a stage of disease without active inflammation.

Invasive examinations are still important in most patients with suspected cardiac sarcoidosis. Coronary angiography will exclude coronary heart disease. Myocardial biopsies are recommended to provide histological proof of suspected cardiac involvement. These biopsies are normally taken from the myocardium of the right ventricle, though the most frequently affected area is in the myocardium of the left ventricle. Most biopsies consequently give false-negative results, leading to an unacceptably low success rate for myocardial biopsies of around 25%.[10,11,18]

Only a few studies with small numbers of patients predict that F-18 FDG-PET may be useful in cardiac sarcoidosis. Accumulation of F-18 FDG in inflammatory areas of the myocardium has demonstrated higher sensitivity for the detection of myocardial lesions than Tl-201 or Ga-67 scintigraphy.[16] Its specificity for the diagnosis of cardiac sarcoidosis has yet to be confirmed, though.

BENEFITS OF MRI

Cardiac MRI appears to be the most valuable tool for tissue characterization. Detection of cardiac sarcoidosis was described in a few case reports prior to the late 1990s as intramyocardial signal intensity on T2-weighted MRI due to edema and inflammation. A study in 2001 reported localized contrast-enhanced myocardial areas in eight out of 16 patients with known cardiac sarcoidosis.[19] Research published the following year showed the usefulness of MRI in monitoring the efficacy of steroid therapy by detecting lesion shrinkage.[20]

MRI assessment of cardiac sarcoidosis has benefited from use of the delayed enhancement technique, performed 15 to 20 minutes after administration of gadolinium-DTPA (Figures 1 through 4). This has enabled MRI to provide additional information, especially when myocardial biopsy or other imaging approaches prove inconclusive. The inherent soft-tissue contrast, especially after intravenous contrast administration, generates a high sensitivity for myocardial tissue abnormalities. Irreversibly injured myocardium with fibrosis or necrosis can then be visualized accurately by delayed enhancement imaging.[20-25]

The high spatial resolution of MRI allows a more precise evaluation of the heart tissue than is available with other modalities. Myocardial thinning and thickening and wall motion abnormalities can all be detected with MR. Tissue abnormalities induced by sarcoidosis demonstrate a pattern on delayed enhancement imaging similar to that of lesions induced by myocardial ischemia, though the distribution is not related to coronary vascular territories.

Hyperkinesias of the affected myocardial areas are quite common.[26,27] In particular, involvement of the interventricular septum is a typical finding. The origin of ventricular tachyarrhythmias and wall motion abnormalities,

along with delayed enhancement, indicates that sarcoidosis has affected the myocardium (the term origin here means the point of origin from which these tachyarrhythmias emerge; i.e., from infiltrations in the His-Purkinje system). The underlying ventricular tachyarrhythmias in sarcoidosis are interpreted as a reentry mechanism with involvement of the His-Purkinje system. Because tachyarrhythmias occur only occasionally, MRI quality is not hampered substantially. MRI may be unhelpful in patients with pacemak-
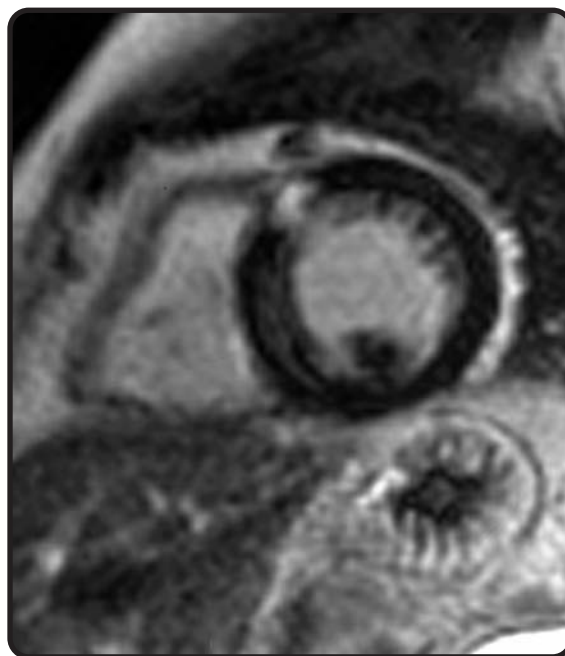

FIGURE 3. Short-axis contrast-enhanced 3D turbo flash sequence (TR 750/TE 4.5/TI 210 msec) reveals anteroseptal delayed enhancement.

ers or an implantable cardioverter-defibrillator.

Cardiac MRI is a rapid, high-resolution, noninvasive method of screening for myocardial involvement and fibrosis occurring in cardiac sarcoidosis. We perform the technique on a 1.5T scanner (Magnetom Sonata Maestro Class, Siemens Medical Solutions) using a body surface coil and spine coil. T1-weighted multislice multiphase turbo spin-echo sequences are used to visualize the entire mediastinal

area. Short-axis views covering the entire heart and four-chamber views are performed using the following protocol:

• T2-weighted MRI with breath-hold turbo inversion recovery sequence. Inversion time: 170 msec for fat suppression;

• TrueFISP cine sequence used for dynamic left ventricular analysis. Contiguous short-axis views cover both ventricles. Additional three- and four-chamber views also performed;

• 3D turbo flash sequence for delayed enhancement imaging. Inversion time individually optimized in short and long axes; and

• 3D turbo flash sequence for delayed enhancement imaging performed using an optimized inversion time of 210 msec in short and long axes.

The Japanese Ministry of Health and Welfare has provided guidelines to assist in the diagnosis of cardiac sarcoidosis.[28] These guidelines need to be supplemented with criteria from MRI, given the modality's superior temporal and anatomical resolution.

TREATMENT REGIMEN

Treatment of cardiac sarcoidosis consists of corticosteroid application, antiarrhythmic treatment, implantation of pacemakers and defibrillators, and, ultimately, a heart transplant.

Controversy over the dose and duration of corticosteroid treatment is ongoing. Corticosteroids are believed to work by reestablishing the balance between type 1 and type 2 helper cells. They should halt progression of cardiac infiltration and improve survival time but have no effect on

cardiac arrhythmias. Corticosteroid treatment has been linked, however, to the incidence of ventricular aneurysms, which brings a risk of further arrhythmias. Antimalarial drugs and arthritis drugs methotrexate and azathioprine could provide alternatives to corticosteroid therapy.

Additional application of antiarrhythmic agents is often essential, yet their effectiveness has not been documented. Some of the agents have notable side effects, so treatment with them has to be carefully considered. Beta blockers, for example, can increase the risk of heart blocks.

Pacemaker and/or defibrillator implantation may become necessary, especially in patients with a high risk of refractory ventricular tachyarrhythmias. Some clinicians recommend defibrillator implantation in all patients with cardiac sarcoidosis and ventricular tachyarrhythmias. Organ transplantation is rare, owing to the likely recurrence of cardiac sarcoidosis in the new heart. It remains an option, though, particularly for young patients.

Early diagnosis of cardiac sarcoidosis is challenging but vital. Prognosis is likely to be poor once the disease reaches an advanced stage. Several diagnostic options exist, but none is approved as a gold standard by attending physicians.

Combination of these options, together with knowledge of clinical presentation, may allow the disease to be diagnosed earlier. Cardiac MRI and FDG-PET are the most valuable tools to date, having higher sensitivity than alternative methods. Improvements in the early diagnosis of cardiac sarcoidosis may rest with these two imaging modalities. ■

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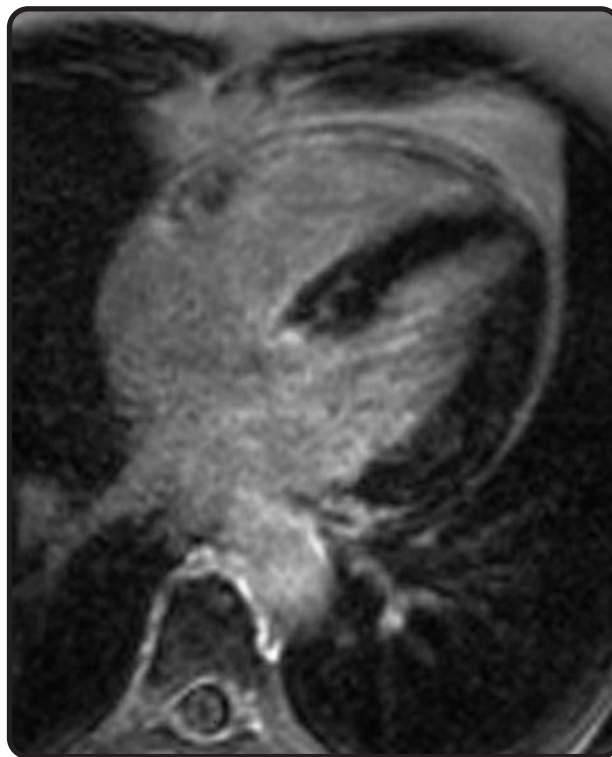
FIGURE 4. 3D turbo flash sequence (TR 750/TE 4.5/TI 210 msec) in two-chamber view shows anteroseptal delayed enhancement, as well as anterior right and left ventricular hyperenhancement.

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