



## CASE STUDY

# Detecting cardiac involvement in sarcoidosis: a call for prospective studies of newer imaging techniques

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**ABSTRACT:** Diagnosis of cardiac involvement in sarcoidosis is challenging and usually relies on a combination of clinical findings and imaging abnormalities.

The case of a 53-yr-old female is described who presented with ventricular tachycardia and suspected angiosarcoma involving the right atrium and superior vena cava.

A combination of magnetic resonance imaging and <sup>18</sup>F-2-fluoro-2-deoxyglucose-positron emission tomography were essential to the diagnosis of cardiac sarcoidosis.

Reversibility of the disease was predicted more clearly by <sup>18</sup>F-2-fluoro-2-deoxyglucose-positron emission tomography than by magnetic resonance imaging, and clinical activity was predicted by persistent hypermetabolism on serial <sup>18</sup>F-2-fluoro-2-deoxyglucose-positron emission tomography.

**KEYWORDS:** Cardiac arrhythmias, granulomatosis, imaging, magnetic resonance imaging, positron emission tomography, sarcoidosis

Despite an expanding array of technologies, identifying myocardial involvement in sarcoidosis is one of the most challenging aspects of the disease. While symptomatic cardiac involvement is evident in only 2–7% of patients from the USA, up to 25% of patients have granulomatous involvement at necropsy [1, 2]. Sudden death due to unsuspected cardiac involvement occurs in as many as 35% of affected individuals [2]. Even if the diagnosis is suspected, conventional imaging techniques may be insensitive to the detection of myocardial involvement. A distinct but related problem is determining whether dysrhythmias, conduction delays or cardiomyopathies reflect active myocardial inflammation or only scarring. Delayed treatment or undertreatment may pose substantial risks [3], yet it is unclear how to discern whether a treatment is efficacious or unnecessary.

Electrocardiography, echocardiography, gallium imaging and myocardial perfusion imaging with radioactive tracers have all previously been used to diagnose cardiac sarcoidosis. Since the mid 1990s, the use of several new imaging techniques has been described. These include delayed enhanced cardiac magnetic resonance imaging (MRI) and <sup>18</sup>F-2-fluoro-2-deoxyglucose-positron emission tomography (FDG-PET) [4, 5].

The present authors recently treated an individual in whom the diagnosis of cardiac sarcoidosis was elusive, requiring the complementary use of cardiac MRI with PET myocardial perfusion and metabolic imaging with rubidium-82 and FDG. The present case study exemplifies the potential utility of these newer imaging techniques for addressing the clinical uncertainty of diagnosis and treatment decisions in cardiac sarcoidosis.

### CASE REPORT

A 53-yr-old Caucasian female with a history of hypertension was referred to the present authors' facility in December 2003 for recurrent episodes of ventricular tachycardia (VT) refractory to treatment with high-dose verapamil, mexiletine and radiofrequency catheter ablation. Coronary angiography was unremarkable but a cardiac MRI suggested the possibility of a mass in the right atrium and superior vena cava, thought to be an angiosarcoma. MRI was repeated at the present authors' institution. In addition to standard static- and cine-sequences for the assessment of ventricular anatomy, myocardial perfusion was assessed using T1-weighted, multislice, spoiled-gradient echo images obtained during first pass of 0.1 mmol·kg<sup>-1</sup> gadolinium-diethylenetriaminepentaacetic acid (Gd-DPTA).

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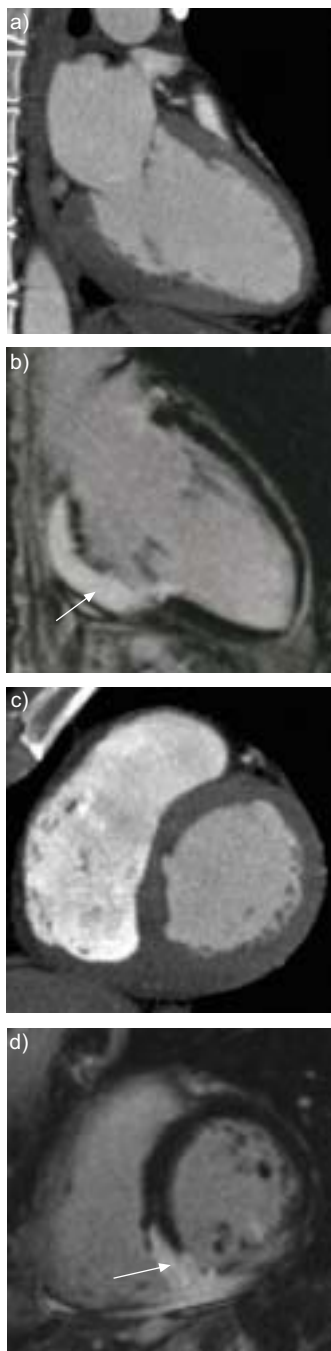
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### STATEMENT OF INTEREST

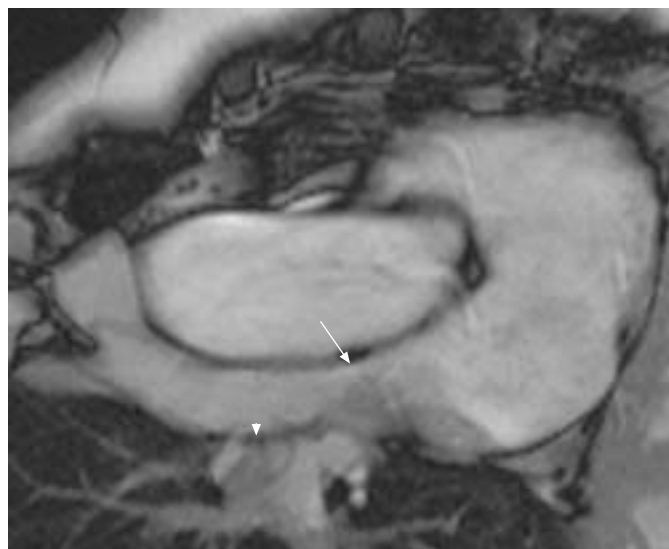
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**FIGURE 1.** a, b) Two-chamber and c, d) short axis view of the left ventricle. Infiltration of the basal inferior myocardial wall is clearly shown on delayed contrast enhanced magnetic resonance images (arrows). a) and c) show the corresponding computed tomography images.

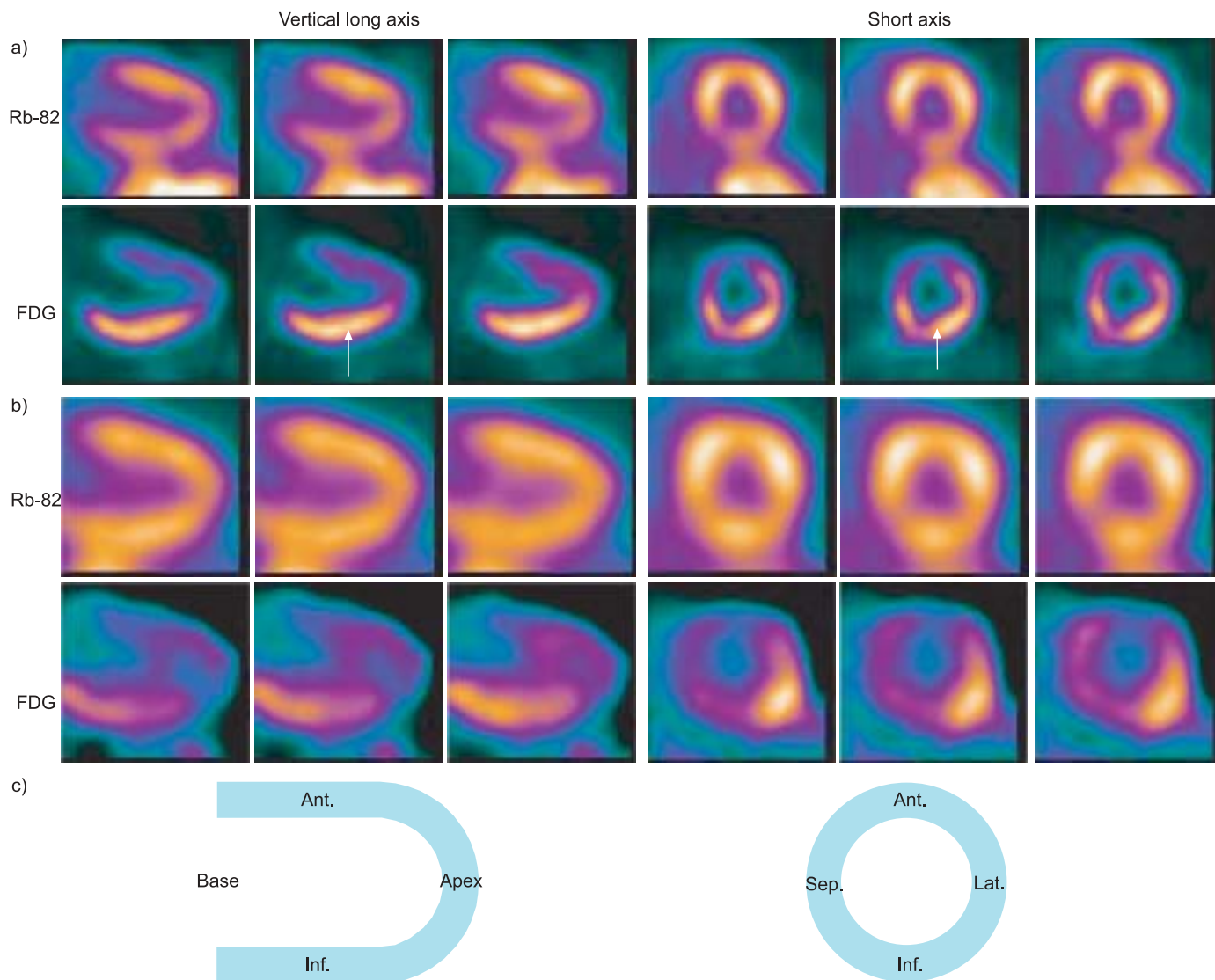
Delayed enhancement was then assessed 15 min after infusion of an additional  $0.1 \text{ mmol}\cdot\text{kg}^{-1}$  infusion of Gd-DPTA using an inversion recovery spoiled gradient echo sequence. The study confirmed the presence of a mass-like structure in the right atrium but also showed mediastinal and hilar lymphadenopathy, and an infiltrative process involving the basal inferoseptal and inferior left ventricle (LV), the inferior wall of the right ventricle, the posteromedial papillary muscle, and scattered endocardial foci in the lateral wall and septum of



**FIGURE 2.** Lentiform mass (arrow) visualised along the right postero-lateral endocardial surface of the right atrium and superior vena cava. Right hilar lymphadenopathy (arrowhead) is also present.

the mid-apical region of the LV (figs 1 and 2). Enhanced signal on the delayed images suggested that the myocardial involvement represented fibrosis. Based on these new findings, angiosarcoma was deemed unlikely. Cardiac PET perfusion imaging with rubidium-82 revealed perfusion defects in the mid-to-basal inferior, basal inferolateral, basal inferoseptal of the LV and the adjacent right ventricular myocardium, paralleling the predominant MRI findings (fig. 3). Enhanced FDG uptake, suggesting an inflammatory granulomatous process, was noted in the hypoperfused areas and was most striking in the inferolateral region. The perfusion–metabolism mismatch was slightly less pronounced in the inferoseptal area.

Chest computed tomography (CT) and whole body FDG-PET imaging revealed hypermetabolic lymph nodes in the chest, abdomen, right thyroid lobe and iliac crest; mediastinoscopy confirmed the diagnosis of sarcoidosis. Treatment consisted of sotalol, prednisone, methotrexate  $20 \text{ mg}\cdot\text{week}^{-1}$  and placement of an implantable automated cardioverter-defibrillator (AICD). The VT episodes resolved completely within 6 weeks. The right atrial mass, most probably an intracardiac manifestation of sarcoidosis, was completely resolved on echocardiographic examination. Repeat cardiac rubidium-82 FDG-PET images in May 2004 demonstrated a persistent but marked decrease in the extent of the left ventricular myocardium with perfusion–metabolism mismatches. There was a focal persistent hypermetabolic defect in the basal inferolateral myocardium (fig. 3). Since the implications of this perfusion–metabolism defect were uncertain, the steroid dose was tapered to  $5 \text{ mg}\cdot\text{day}^{-1}$  and methotrexate  $15 \text{ mg}\cdot\text{week}^{-1}$  continued. In December 2004, the patient developed recrudescence of symptomatic VT and a third rubidium-82 FDG-PET study demonstrated interval worsening of mismatched perfusion–metabolism defects in the same areas of the left ventricle. Leflunomide  $20 \text{ mg}\cdot\text{day}^{-1}$  was added to the patient's regimen, along with a steroid taper ( $40 \text{ mg}\cdot\text{day}^{-1}$  to  $10 \text{ mg}\cdot\text{day}^{-1}$  over 3 months). Within 2 months,



**FIGURE 3.** Rubidium (Rb)-82 perfusion images and  $^{18}\text{F}$ -2-fluoro-deoxyglucose (FDG) metabolic images a) prior to treatment (December 2003) and b) following medical therapy (May 2004). c) Anatomic orientation of the images. The areas of perfusion–metabolism mismatch (arrows) are less pronounced following therapy, paralleling resolution of the patient’s symptomatic episodes of sustained ventricular tachycardia. Ant: anterior; Inf: inferior; Sep: septum; Lat: lateral.

the patient’s symptomatic VT episodes resolved. A fourth PET scan in May 2005 showed only faint FDG uptake but persistent perfusion defects, and a contemporaneous multidetector cardiac CT scan confirmed the suggestion of scarring, with a pattern of low attenuation and thinning of the inferoseptal and inferior myocardium. Currently, the patient experiences very rare episodes of asymptomatic nonsustained VT only, on a maintenance regimen of leflunomide  $20\text{ mg}\cdot\text{day}^{-1}$ , prednisone  $5\text{ mg}\cdot\text{day}^{-1}$  and sotalolol.

## DISCUSSION

As yet, the clinical role of emerging technologies, such as delayed-enhanced cardiac MRI and PET imaging, for diagnosing cardiac sarcoidosis is undefined. The present case suggests that the two imaging modalities may provide complementary diagnostic information and illustrates several of the most salient issues surrounding cardiac sarcoidosis.

Foremost among these is the proliferation of available imaging modalities. No study has prospectively ascertained the accuracy of each of the various techniques for diagnosing myocardial involvement in patients with suspected cardiac sarcoidosis. The clinician is left with little guidance about which test to choose, or worse still, is dependent on the vagaries of insurance approval. With the expanding array of technologies, it is important to know which is the most accurate and cost-effective approach.

Historically, thallium scintigraphy, gallium scanning and echocardiography have been widely used when cardiac sarcoidosis is suspected. More recently, the usefulness of cardiac MRI has been recognised, with the advantages of increased accuracy and the possibility of identifying areas of “reversible” active inflammation and “irreversible” scarring based on the pattern of gadolinium enhancement [4]. In a series of 10 subjects with clinically diagnosed cardiac disease,

MRI sensitivity was 100% versus 50% for thallium single photon emission CT (SPECT) and only 20% for gallium SPECT [6]. A similar study in the Netherlands also suggested higher sensitivity of cardiac MRI [5]. One current limitation of cardiac MRI is that it cannot be used for imaging in patients with indwelling cardiac devices, such as AICDs or pacemakers. It is noteworthy that recent reports have demonstrated that conventional MRI may be safely used with certain device models [7], suggesting that MRI may be a viable tool for following disease activity in selected patients. A major advantage of MRI compared with FDG-PET is cost. At present, however, the presence of pacemakers or defibrillators remains a contraindication to MRI, pending further delineation of the risk-benefit ratio.

The largest series to address the diagnostic accuracy of cardiac PET imaging with FDG compared 11 Japanese subjects, who met the Japanese Ministry of Health and Welfare criteria for myocardial sarcoidosis, and 11 subjects without cardiac involvement [8]. Diagnostic accuracy for FDG-PET, thallium-201 SPECT and gallium scan were 96, 82 and 68%, respectively, with excellent specificity for all three tests. However, sensitivities were only 64% (seven out of 11) and 36% (four out of 11), respectively, for thallium SPECT and gallium scanning compared with 100% for FDG-PET. Complementary use of FDG-PET and perfusion scanning with  $^{13}\text{N-NH}_3$  was reported by YAMAGISHI *et al.* [9] in a series of 17 patients with cardiac sarcoidosis. In these patients, the perfusion defects demonstrated little change following steroid treatment, while the FDG abnormalities largely resolved. This suggests that with effective treatment, there was progression from an active inflammatory granulomatous process to a healed scar. The use of cardiac PET imaging with rubidium-82 and FDG has not previously been reported in the diagnosis of cardiac sarcoidosis. In the present authors' patient, the PET images showed perfusion-metabolism mismatches in the areas of myocardium probably affected by sarcoidosis, with the area of the most profound mismatch corresponding to the treatment-responsive segments. In contradistinction, the segments that were apparently unresponsive to treatment had a less-pronounced perfusion-metabolism mismatch on FDG-PET and corresponded to the areas with the most striking delayed enhancement on baseline cardiac MRI. These areas eventually developed myocardial thinning on cardiac CT, consistent with scarring.

Another significant issue is the lack of outcome data in well-defined cohorts managed using strategies dictated by the findings on imaging modalities. For example, is it harmful not to treat minor asymptomatic imaging findings? In the largest cohort addressing this question, KINNEY and CALDWELL [10] observed that the presence of asymptomatic thallium-201 scintigraphy defects in a cohort of patients with suspected cardiac sarcoidosis was not associated with increased mortality over a mean follow-up period of 89 months. However, the chance of a type II error seems high, since only 22 untreated patients with positive findings were included. The experience in the present patient suggests that persistent hypermetabolic defects warrant consideration of further treatment, especially in the setting of prior cardiac symptoms. MRI has the potential to identify asymptomatic abnormalities in a subset of patients who otherwise fail to meet strict criteria for myocardial

sarcoidosis [5]; whether the natural history of the disease is altered by treating these findings is unknown. However, it appears that identification of early gadolinium enhancement portends a high chance for progression of the imaging findings at 1 yr [11].

Since endomyocardial biopsy is relatively insensitive in identification of myocardial involvement, noninvasive imaging studies may continue to be key to the diagnosis of cardiac sarcoidosis. Delayed enhanced cardiac MRI [5, 6], cardiac PET imaging with FDG [8], contrast-enhanced multidetector CT [5], ultrasonic tissue characterisation [12], iodine-123-labeled 15-(*p*-iodophenyl)-3*R,S*-methylpentadecanoic acid scintigraphy [13] and combinations of these imaging tests [3] have all been introduced as potential tools, but there are limited data available to define their sensitivity, specificity or predictive value.

The present case supports the findings of ISHIMARU *et al.* [14], indicating that cardiac positron emission tomography imaging with  $^{18}\text{F}$ -2-fluoro-2-deoxyglucose and delayed-enhanced cardiac magnetic resonance imaging may provide complementary information for the diagnosis of cardiac sarcoidosis. The role of these imaging studies in the follow-up and titration of therapy awaits prospective clinical trials with defined treatment algorithms. Until then, clinicians will continue to grapple with these challenging cases. With the explosion of new imaging technologies challenging the ability to investigate their utility in a relatively low prevalence disorder, well-designed prospective multi-institutional studies are desperately needed.

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