Advanced Imaging of Cardiac Sarcoidosis

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Abstract Sarcoidosis with cardiac involvement is underdiagnosed and can put patients at risk of morbidity including conduction defects, arrhythmias and heart failure, as well as sudden cardiac death. In addition, cardiac sarcoidosis may have no clinical manifestations or non-specific presentation and diagnosis may be difficult on clinical criteria. Investigation for cardiac sarcoidosis should be considered in those with extra-cardiac sarcoidosis and cardiac findings as well as those under the age of 60 years presenting with atrioventricular block without a clear cause. Advanced imaging modalities including cardiac magnetic resonance and positron emission tomography may help in both the diagnosis and assessment of response to treatment for cardiac sarcoidosis. This ultimately may help to minimize associated adverse outcomes from this enigmatic disease.

Keywords PET · MRI · Cardiac sarcoidosis · ?Nuclear imaging

Introduction

Sarcoidosis is a multisystem inflammatory disease with characteristic non-caseating granulomas on histopathology [1]. The lungs and pulmonary lymph nodes are most commonly affected, but the heart and other tissues including skin, eyes, central nervous system, liver, spleen and skeleton can also be involved [2–7]. The aetiology of sarcoidosis is not well understood. It is most likely to be multifactorial with environmental triggers precipitating an immune response and granulomatous inflammation in susceptible individuals with a polygenic predisposition [3, 8, 9].

Sarcoidosis can occur at any age, with peak incidence at 20–39 years [10]. Although it affects all racial groups, a likely genetic component is reflected by the predominance of the disease in certain populations; incidence of sarcoidosis in white Americans approximates 10 per 100,000 per annum, compared to 35 per 100,000 in African Americans [10].

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Scandinavians have the highest annual incidence rates with reports of 55–64 cases per 100,000, whereas rates of 10–20 per 100,000 are seen across Europe and ≤6 per 100,000 in Asia [11].

Cardiac Sarcoidosis The heart is the third most commonly affected organ in sarcoidosis [2]. Johns and Michele reported that only up to 7 % of patients with systemic sarcoidosis had cardiac symptoms or clinical manifestations [12]. Autopsy series describe higher rates of myocardial involvement, ranging from 27 to 47 % [1, 4, 13]. Clinical imaging studies also describe prevalence rates between 19 and 55 % for asymptomatic cardiac sarcoidosis (CS) in patients with extra-cardiac sarcoidosis [14••, 15••, 16–18]. The typical pathology in CS is patchy oedematous and granulomatous infiltration of the myocardium. The active, inflammatory phase may subside or progress to fibrosis [1, 3].

Cardiac disease worsens prognosis and is an important cause of mortality in sarcoidosis patients, although pulmonary sarcoidosis has been reported as the most common cause of death from sarcoidosis in Caucasians [3, 4, 13]. Japanese studies have observed the highest rates of cardiac involvement and adverse outcome in their population. It has been reported that 67 % of patients with systemic sarcoidosis in Japan have CS, and up to 85 % of deaths are attributed to CS [13, 19–21]. One Japanese study has observed overall mortality rates in CS of 40 % at 5 years [20]. In our meta-analysis of CS patients treated with corticosteroids, 5-year mortality rates ranging between 0 and 25 % were observed [22••].

Clinical Aspects CS is usually clinically silent and often is detected on screening of patients with systemic sarcoidosis. It may have variable clinical manifestations which depend on the stage, degree and location of disease. Presentations can range from conduction disturbances (most commonly), supraventricular and ventricular arrhythmias, left and/or right heart failure, pericardial effusion and sudden death [1, 6, 9, 23, 24••].

Electrical manifestations of CS are clinically significant [25••]. Nery et al., in a series of consecutive patients aged ≤60 years, showed that 34 % of those with unexplained atrioventricular block had previously undiagnosed CS, and were more likely to have adverse outcomes than those without CS [24••]. Kandolin et al. in a 72 patient Finish study have also shown CS is common in patients with unexplained AV block, occurring in 19 % of cases [26••]. Patients with CS may experience ventricular tachycardia (VT) and ventricular fibrillation (VF). Betensky and colleagues observed an incidence of 15 % per year on long-term follow up in those with biopsy-proven sarcoidosis and cardiac involvement confirmed by clinical criteria, and/or advanced imaging, and/or cardiac biopsy [27••].

Ventricular tachyarrhythmias and atrioventricular block account for 30–65 % of deaths in patients with CS [2]. Extent of left ventricular (LV) dysfunction, worse New York Heart Association functional class, LV dilation and history of VT have been shown to be predictors of mortality [20, 22••]. CS should be considered and ruled out in all patients diagnosed with extra-cardiac sarcoidosis and in all patients under the age of 60 with unexplained advanced atrioventricular block [24••, 25••].

Treatment with corticosteroids may improve outcomes in patients with active CS, with modest data to support its use [22••, 28]. There may be a role for steroid-sparing immunosuppression (e.g. methotrexate, azathioprine). However, no current therapies for cardiac sarcoidosis are validated by randomized control trials. There is an important role for pacemaker devices for those with advanced conduction abnormality, and prophylactic implantable cardiac defibrillator (ICD) devices can be lifesaving in those at risk of ventricular arrhythmia [25••, 29]. The 2014 Heart Rhythm Society (HRS) consensus statement offers comprehensive guidelines for prophylactic ICD implant, with recommendations ranging from class I to class IIb depending on clinical and imaging findings [25••]. For all these reasons, it is important to accurately diagnose CS early [5].

Diagnosis Diagnosis of CS can be challenging, particularly in the early stages of disease. Myocardial biopsy, considered to be the gold standard when positive, is highly specific but is invasive and has poor sensitivity with a diagnostic yield as low as 19 % [2, 30]. This is because cardiac involvement is not homogeneous and lesions are usually in a patchy distribution. Lesions predominate in the basal and mid interventricular septum and are patchy elsewhere [5, 6, 16], whereas biopsy sampling tends to be acquired from along the right side of the septum [17]. Cardiac biopsy cannot effectively rule out disease. Newer techniques such as voltage guidance may increase the yield of endomyocardial biopsy [31].

Although positive biopsy is definitive, the poor sensitivity means that currently, the diagnosis of CS is most often made using clinical criteria. Until recently, the Japanese Ministry of Health and Welfare (JMHW) guidelines have been used as the best available standard and take into account invasive tissue diagnosis, and electrical, functional and structural abnormalities noted on electrocardiography, echocardiography, nuclear imaging or cardiac magnetic resonance (CMR) imaging [32]. However, some data have suggested that these criteria have low sensitivity [30] and may fail to detect early signs of cardiac involvement [33]. JMHW criteria presently do not give heavy weighting to modern advanced cardiac imaging modalities, with gadolinium-enhanced CMR added as a minor criterion in the 2006 revision and positron emission tomography (PET) not included in the current JMHW algorithm.

The recent collaborative consensus statement from the Heart Rhythm Society (HRS) and others does however recognize the role of advanced imaging with PET and CMR in the diagnostic workup for CS (Table 1) [25••]. The HRS expert consensus provides the current accepted criteria for the diagnosis of CS. Advanced cardiac imaging holds much promise in the identification and surveillance of CS. CMR and PET are the tests of choice in most centres that have access to them. Whilst they are not optimal modalities for diagnosis of CS, there are features on echocardiography and cardiac CT that may corroborate diagnosis. This review will address each of the imaging modalities for CS.

Echocardiography

Abnormalities on echocardiography have been described in up to 13–31 % of patients with systemic sarcoidosis and in 46 % of those with CS [6, 17, 34, 35]. There are no definite findings on echocardiogram that may confirm CS, but there are changes that may be consistent with the diagnosis. Additional tests are required to establish or exclude a diagnosis of CS. The most common echocardiographic abnormalities in

Table 1 Criteria for diagnosis of cardiac sarcoidosis

HRS expert consensus recommendations on criteria for the diagnosis of CS, 2014

Two pathways to diagnose CS

• Histological diagnosis from myocardial tissue: CS is diagnosed in the presence of noncaseating granuloma on histological examination of myocardial tissue with no alternative cause identified

• Clinical diagnosis from invasive and noninvasive studies

  It is probable (considered adequate to establish a clinical diagnosis of CS) if:

    a) There is a histological diagnosis of extracardiac sarcoidosis and

    b) One or more of the following is present:

      • Corticosteroid- and/or immunosuppressant-responsive cardio-myopathy or heart block

      • Unexplained reduced LVEF (<40 %)

      • Unexplained sustained (spontaneous or induced) ventricular tachycardia

      • Mobitz type II second-degree heart block or third-degree heart block

      • Patchy uptake on dedicated cardiac positron emission tomography (PET; in a pattern consistent with CS)

      • Late gadolinium enhancement (LGE) on cardiovascular magnetic resonance (CMR; in a pattern consistent with CS)

      • Positive gallium uptake (in a pattern consistent with CS)

  and

    c) Other causes for the cardiac manifestation(s) have been reasonably excluded.

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patients with CS are septal wall thinning or thickening, systolic and diastolic dysfunction and wall motion abnormalities [34, 35]. Pericardial effusion and mitral regurgitation can rarely be present.

Echocardiography can determine LV cavity size, which has prognostic implications in that LV dilatation is strongly associated with increased mortality [20]. However, early, localized or limited disease often does not have changes that can be seen on echocardiogram. Recent studies suggest that speckle tracking strain echocardiography may have a role in assessment of CS, as patients with structural lesions have a drop in global longitudinal and circumferential strain parameters [36, 37]; however, more and larger studies are needed to determine its clinical role.

Nuclear Perfusion Imaging

Radionuclide studies have been commonly used to identify cardiac disease in patients with sarcoidosis. These include single photon emission CT (SPECT) myocardial perfusion imaging (MPI) with thallium-201(Tl-201) or technetium-99m (Tc-99m) and gallium-67 (Ga-67) scintigraphy [9]. Resting perfusion scans using Tl-201 or Tc-99m based MPI may show decreased tracer uptake in areas of damaged myocardium representing fibrotic or granulomatous tissue; this may correlate with heart block and tachyarrhythmia [8, 9, 38].

Sensitivity of Tl-201-based MPI in patients with clinical suspicion of CS has been reported at 45 and 58 % in small studies, whereas sensitivity for Tc-99-based MPI studies has been reported at 65 % [39, 40]. Abnormality on Tl-201 MPI in patients with systemic sarcoidosis who do not have cardiac symptoms has not been shown to have prognostic value [41]. 'Reverse redistribution' is a finding sometimes seen in patients with CS described on Tl-201 and Tc-99m-based MPI, where focal perfusion defects on rest imaging improve or disappear altogether on stress imaging, which is opposite to the pattern seen in ischaemia caused by coronary artery stenosis [42, 43]. This has been hypothesized to be due to focal reversible vasoconstriction in arterioles adjacent to sarcoid granulomas [44].

Ga-67 scintigraphy displays 'hot spots' in areas of active inflammation and has the advantage of being able to diagnose both pulmonary and systemic sarcoidosis, as well as assess disease activity and effect of treatment [45, 46]. Ga-67 scanning has high specificity (reported at nearly 100 %); however, its image resolution is low and has much lower sensitivity (reports ranging from 18 to 50 %) than other radionuclide tests [40, 42, 47, 48]. Whilst Ga-67 scintigraphy is excellent in detection of inflammation, it may not identify areas of fibrosis and may miss quiescent disease.

FDG PET is more accurate in detecting myocardial abnormalities than Tc-99m MPI and Ga-67 SPECT in sarcoidosis
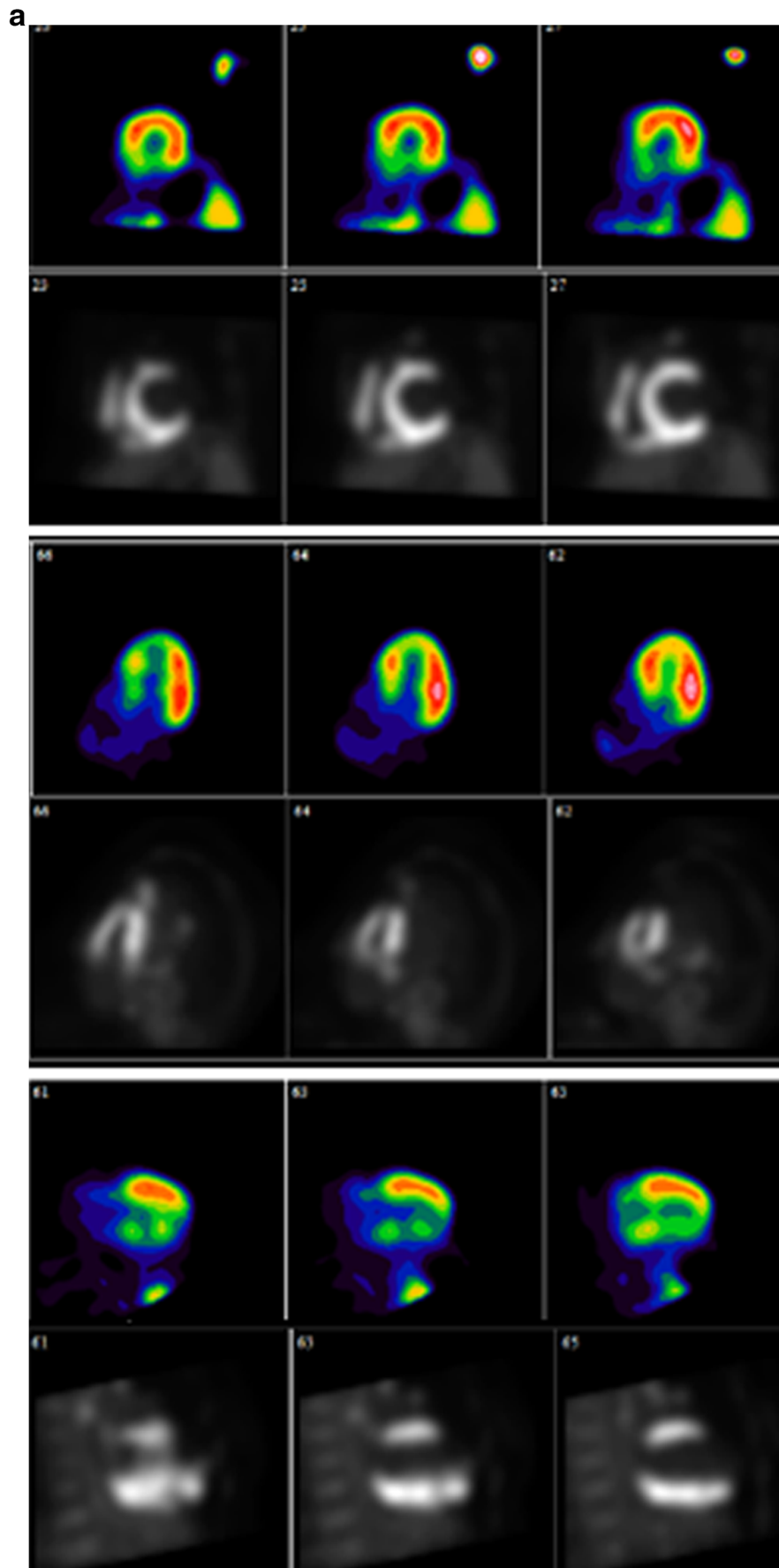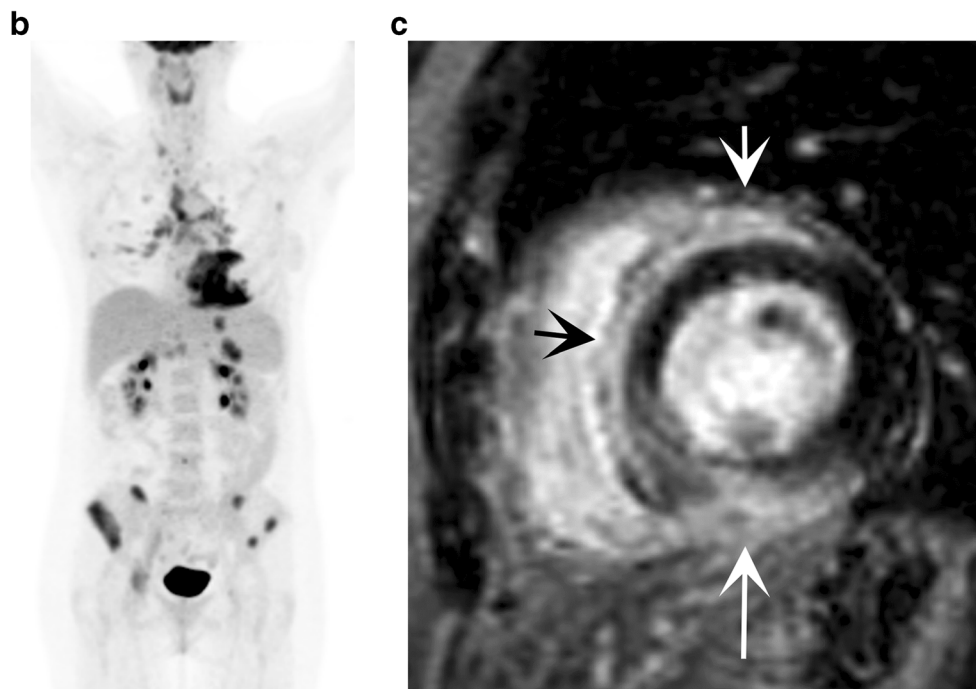
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Fig. 1 (continued)

patients [48–50]. In centres where PET or CMR are available, these newer imaging techniques have mostly replaced other radionuclide imaging.

Computed Tomography

Cardiac computed tomography (CT) angiography can be helpful to exclude coronary artery disease in patients being assessed for cardiac sarcoid. Additionally, there are case

◄ **Fig. 1** 54-year-old female presented with ventricular tachycardia and complete heart block requiring emergent temporary pacing, with subsequent implant of ICD for secondary prevention. Endomyocardial biopsy demonstrated non caseating granuloma, confirming the diagnosis of CS. CMR and PET imaging performed at time of diagnosis are shown below. **a** PET study with focal intense uptake of FDG tracer (*black and white panels*) in the basal and inferior septum and inferior wall, with partially corresponding areas of reduced perfusion on rubidium-82 PET images seen in the basal septum and inferior wall (*upper panels*). These metabolically active areas on PET represent active inflammation due to CS, and in this case, parallel enhancement on CMR. Note RV uptake is present. **b** Whole body PET image, depicting multifocal hypermetabolic lesions in the heart, as well as extra-cardiac active inflammation from sarcoidosis in the pulmonary, mediastinal and hilar lymph nodes. Uptake in the kidneys, urinary bladder and gut are physiological. **c** Late gadolinium enhancement magnitude inversion recovery image in the short axis oblique plane of the same patient shows typical linear enhancement in the septum and subepicardial anterior wall (*short arrows*), as well as almost transmural enhancement in the inferior wall (*long arrow*). Note the enhancement in the right ventricular side of the septum (*black arrow*), a characteristic finding in cardiac sarcoid

reports that describe findings on cardiac CT in patients with CS. Late contrast-enhanced cardiac CT images have been reported to demonstrate similar location and extent of enhancement to those of CMR [51, 52]. Generally, fibrosis if large enough can also be seen as areas of hypo-enhancement in the myocardium on rest CT perfusion imaging; however, this is not specific to scar from sarcoidosis.

Furthermore, if retrospective ECG-gated cardiac CT examination is performed, relevant findings may also be detected such as wall motion abnormalities, decreased LV ejection fraction (LVEF) and/or morphological abnormalities (aneurysms, myocardial thinning or thickening), all of which may help to support the diagnosis of CS, but at the expense of increasing radiation dose.

Screening for characteristic pulmonary parenchymal abnormalities and enlarged mediastinal and hilar lymph nodes in an extended field of view reconstruction should be performed when Sarcoidosis is suspected. It should be noted that the recent consensus statement from HRS recommends high resolution CT of the thorax be performed in patients <60 years old with unexplained advanced AV block [25••].

Cardiac Magnetic Resonance Imaging

Role and Diagnostic Performance Cardiac magnetic resonance with late gadolinium enhancement (LGE-CMR) is emerging as a preferred advanced imaging modality to evaluate CS [16, 53]. CMR is an accurate non-invasive test that

offers both structural and functional information. It has high sensitivity (87.5–100 %), but lower specificity (38.5–78 %) for detecting CS [5, 6]. Smedema et al. reported "positive and negative predictive values of 55 and 100 % respectively, with overall accuracy of 83 %" [6]. Thus, to enable early diagnosis if CS is suspected, recent guidelines recommend advanced imaging with high sensitivity, such as CMR or PET, be performed [25••].

CMR represents an important tool for the early diagnosis and treatment of CS [6]. Due to the high spatial resolution of the LGE techniques, CMR is able to detect even small areas of myocardial damage which may not have yet caused structural or electrical abnormality, and may not be detected by other imaging methods [15••]. Such areas of myocardial damage are clinically relevant as they may be potential substrate for arrhythmias and sudden cardiac death, and they can also be targeted if endomyocardial biopsy is required, to increase its diagnostic yield.

Imaging Techniques and Findings CMR findings depend on the stage of disease. CMR is able to detect the acute inflammatory and chronic phases of CS [54]. These two phases may frequently overlap. During the acute phase, areas of focal wall thickening associated with wall motion abnormalities on steady state free precession (SSFP) CINE sequences may be seen. T2 weighted imaging (T2WI) may show foci of increased signal intensity, indicative of edema and active granulomatous infiltration [55•, 56]. Crouser et al. have also reported that T2 mapping techniques allow quantitative measurement of free water in the myocardium [57], which in the context of CS is presumed to represent granulomatous inflammation [58]. Importantly, recent reports suggest that high myocardial T2 values could represent early stages of disease that may be reversible with appropriate treatment [55•].

Despite useful information provided by T2WI techniques, LGE-CMR has attracted most of the attention of the scientific community in recent years. Gadolinium, an extracellular contrast agent, is depicted as areas of myocardial enhancement (Fig. 1c). It is retained in areas of myocardial damage such as fibrosis and necrosis [59]. LGE may be seen in up to 19–35 % of patients with extra-cardiac sarcoidosis in whom a clinical diagnosis of CS has not been established [6, 14••, 15••, 17, 55•, 60]. Although there is no pathognomonic finding, frequently seen patterns in CS include patchy mid-myocardial, linear sub-epicardial or transmural enhancement.

In CS, LGE is usually in a non-vascular distribution. However, sub-endocardial enhancement in a coronary distribution similar to myocardial infarction has been observed. This pattern can be difficult to differentiate from myocardial infarction caused by ischemic heart disease [14••, 16, 56, 61]. Enhancement in CS has a preference to involve the basal and mid interventricular septum and to a lesser extent lateral LV wall [5, 6, 8, 16]. Interestingly, enhancement in the RV side of the

interventricular septum has been reported as a common pattern present in up to 67 % of CS patients [16]. Typically, transmural enhancement may be associated with myocardial thinning and regional wall motion abnormalities in the chronic phase of the disease [14••, 33, 56].

As noted above for CT imaging, SSFP CINE sequences are able to accurately depict other findings suggestive of CS including morphological abnormalities (aneurysms, myocardial thickening or thinning), wall motion abnormalities as well as LV systolic dysfunction.

As CS is often associated with arrhythmias and cardiomyopathy, in some cases, an important differential to consider is arrhythmogenic right ventricular cardiomyopathy (ARVC). CMR can be very useful to differentiate these two entities. Steckman et al., in a study of 61 patients, observed that those with CS versus ARVC were more likely to have CMR findings of LGE (73 vs 19 %), isolated LV involvement (53 vs 0 %), septal involvement (43 vs 0 %) and mediastinal lymphadenopathy (68 vs 0 %), whereas those with ARVC where more likely to have isolated right ventricular involvement (76 vs 20 %), lower right ventricular (RV) ejection fraction, and larger LV and RV systolic and diastolic volumes [62••]. All patients with ARVC had RV CMR findings [62••].

Prognosis and Monitoring Response to Therapy LGE-CMR is able to detect small scars that may be the substrate of arrhythmias and SCD [6]. There is increasing evidence that the presence of LGE is a robust independent predictor of death and adverse events in patients with suspected CS [6, 14••, 16], with one recent study suggesting the contrary [33]. Thus, the presence of myocardial enhancement is emerging as an important tool for risk stratification. Greulich and colleagues reported hazard ratio (HR) of 31.6 for 'death, aborted SCD, and appropriate ICD discharge' and HR of 33.9 for VT [14••]. Similarly, Patel et al., demonstrated that patients with LGE "had a 9-fold higher rate of major adverse cardiac events (MACE) and 11.5-fold higher rate of cardiac death compared to patients without LGE" (MACE, 17.2 % versus 1.9 % per year; cardiac death, 11.5 % versus 1.0 % per year) [16].

In addition, in at least one study of patients with systemic sarcoidosis without myocardial enhancement, no SCD or VT was observed, even in the presence of dilated LV and severely impaired systolic function. This suggests that LGE on CMR may confer prognostic data beyond that provided by ventricular function alone [14••]. LGE-CMR has also been shown to be useful in assessing response to steroid therapy, as enhancement may improve after treatment and correlate with clinical course [8, 63–65].

Advantages and Limitations CMR has the advantage of wider availability than PET, lack of radiation exposure for patients, and high sensitivity and specificity for the detection of CS. It has high spatial resolution that can enable identification of

small areas of scar. Different techniques are available to help differentiate active and fibrotic phases of CS.

Cardiac devices, such as defibrillators or pacemakers, are often required in patients with CS, but are, in general, contra-indications to CMR. This limits the role of CMR in surveillance for disease progression and effects of treatment. CMR-conditional devices are now available (presently selected pacemakers and implantable loop recorders (ILR) have received CMR-conditional labelling in North America, but no ICD system is approved as CMR-conditional). However, with the CMR conditional devices, image quality may be suboptimal due to artefact. The risks of proceeding with CMR in patients with devices should be carefully balanced with the potential benefit of CMR imaging and assessed on a case-by-case basis. CMR also may miss early inflammation. Whilst T2 imaging may help, it is still associated with technical challenges for the time being.

Positron Emission Tomography

Role and Diagnostic Performance 18-Fluorodeoxyglucose (FDG) positron emission tomography (PET) can also be useful to aid in the diagnosis and follow up of CS. Uptake on FDG-PET suggests active inflammatory process, and steroid treatment has been shown to decrease its size and intensity. The strength of FDG-PET is high sensitivity to detect active CS [5, 50, 66••]. A number of small studies have confirmed its diagnostic accuracy, reporting sensitivity of 81–100 % for detection of CS, with four studies noting a sensitivity of 100 % [5, 48, 50, 67, 68••, 69]. Although studies have reported specificities of 82–91 % [49, 50, 67, 68••], recent reports have observed lower specificity, as low as 39 % [5, 70••]. An explanation for the lower specificity seen in the latter studies may be the ability of PET to detect subclinical CS when compared to JMHW criteria.

We have previously conducted a meta-analysis of seven studies, including the Ontario registry, which included a total of 164 patients, most diagnosed with systemic sarcoidosis, and approximately half with cardiac sarcoidosis [66••]. Pooled data for FDG PET yielded "89 % sensitivity and 78 % specificity, with 4.1 positive likelihood ratio and 0.19 negative likelihood ratio", and overall diagnostic odds ratio was 25.6 [66••]. Our meta-analysis confirms the high diagnostic accuracy of FDG PET to assist in diagnosing CS when compared to JMHW guidelines.

Imaging Techniques and Findings FDG PET uptake assesses active inflammation, which is characterized by increased glucose metabolism, particularly by activated macrophages. Additionally, rubidium-82 (Rb-82) and N-13-ammonia can be used to assess for perfusion defects (PD), which can be caused by fibrous replacement secondary to chronic granulomatous disease [9]. Patterns suggestive of active CS are mainly focal areas of FDG uptake, and focal on top of diffuse uptake [71•]. In patients with CS, FDG uptake is frequently seen in the lungs, lymph nodes and other organs affected by this systemic disease; however, very occasionally, CS can be isolated without systemic sarcoidosis [31].

Normal cardiac uptake of FDG can vary depending on fasting state. Thus, PET scanning protocols aim to suppress physiological uptake of FDG by the myocardium and enable switch to free fatty acid (FFA) metabolism. Methods to suppress normal myocardial glucose uptake include high-fat/low-carbohydrate diet, overnight fast and administration of unfractionated heparin (stimulates lipoprotein lipase which hydrolyzes triglycerides to FFA and glycerol) [71•, 72–75]. Recent advances include attempts at quantification of total volume and intensity of FDG uptake in patients with CS to improve consistency of readings and clinical correlation and prognostication [68••, 76•].

Prognosis and Monitoring Response to Therapy Recent data supports the use of PET for risk stratification in CS and its ability to predict events [68••, 70••]. McArdle et al. demonstrated a correlation between FDG uptake and clinical presentation; patients with CS presenting with VT had significantly higher FDG uptake compared to those with advanced atrioventricular block or if clinically silent [68••]. In addition, maximal FDG uptake was localized to the basal septum in the majority of patients presenting with advanced atrioventricular block [68••].

Most recent findings confirming the prognostic ability of PET have come from Blankstein and colleagues who investigated 118 patients who underwent FDG PET as part of a workup for CS. In this study, 60 % had abnormal PET studies and VT and death were observed in 26 % [70••]. Cardiac PET predicted adverse events, and the presence of both a perfusion defect and abnormal FDG was associated with a hazard ratio of 3.9 [70••]. Their data suggest PET offers prognostic value superior to JMHW clinical criteria, presence of extra-cardiac sarcoidosis and LVEF. Blankstein et al. also noted the importance of RV uptake of FDG, which held a worse prognosis [70••]. Likewise, Manabe et al. demonstrated that when RV uptake was present, patients were more likely to have positive JMHW criteria than when RV uptake was absent, and this difference was more striking than having LV uptake or not [77•].

FDG PET may also have a role to monitor treatment effect and progress in those with CS requiring treatment with corticosteroids. Following treatment with corticosteroids, perfusion defects associated with CS tend to remain unchanged, whereas degree of FDG uptake reduces or resolves with good response to treatment [48]. Osborne and colleagues have also recently shown that reduction in intensity and extent of

myocardial inflammation on FDG PET is associated with improved LVEF and that follow-up PET scanning may help guide therapy [78••]. Although the current available data is promising, large prospective studies are required to better define the clinical role of FDG PET and determine its value for predicting outcome.

Advantages and Limitations FDG PET has the advantage of the ability to well define the active inflammatory phase of CS disease, identify both cardiac and extra-cardiac sarcoidosis involvement (Fig. 1a, b), and follow patients for response to treatment, even if cardiac devices are present. Whilst more sensitive than CMR, it is less specific [5, 59]. Limitations of FDG PET include radiation exposure, albeit small, inadequate

suppression of physiological FDG uptake in normal myocardium can render quality of the study suboptimal, and its low resolution may limit ability to detect small areas of myocardial damage. FDG-PET's lower specificity means there may be difficulty in differentiating CS from other inflammatory diseases.

Future Developments

Given that CMR and PET have unique strengths and weaknesses in assessing different aspects of CS, hybrid imaging may have a role in the future. There are case reports describing
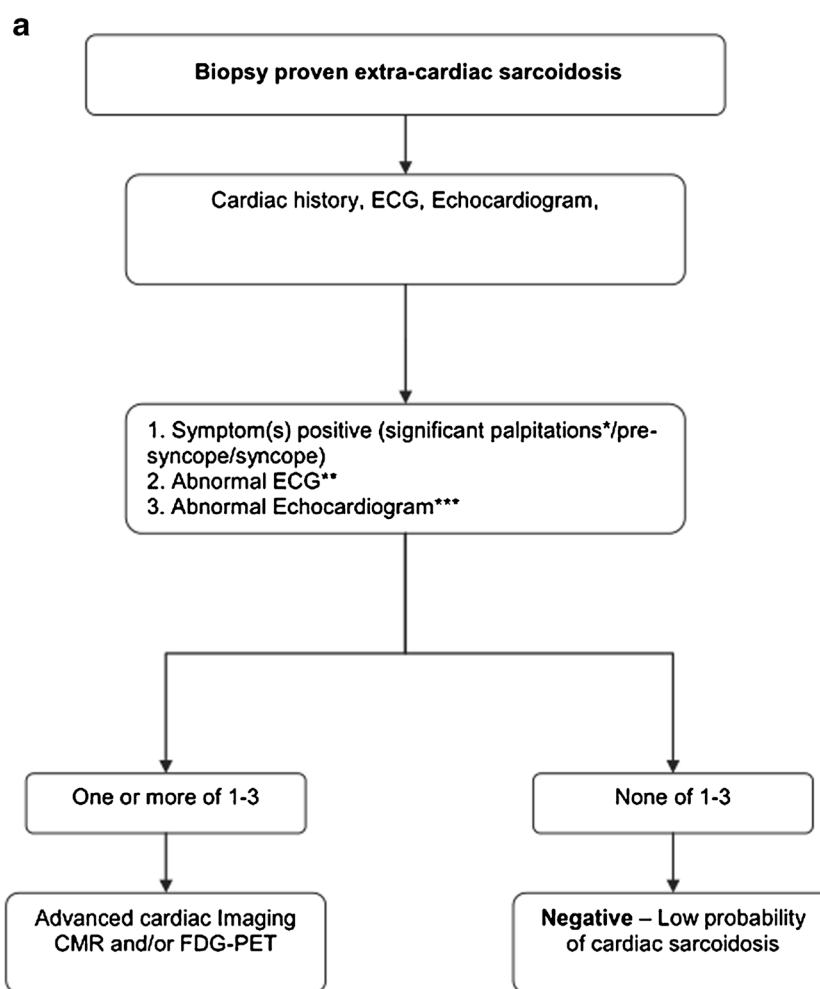
Fig. 2 Diagnostic Algorithm. **a** Suggested algorithm for the investigation of patients with biopsy-proven extracardiac sarcoidosis. *Asterisk* (*) indicates palpitations were defined as "prominent patient complaint lasting >2 weeks." *Double asterisk* (**) indicates abnormal ECG defined as complete left or right bundle branch block and/or presence of unexplained pathological Q waves in two or more leads and/or sustained 2 or 3° AV block and/or sustained or non-sustained VT. *Triple asterisk* (***) indicates abnormal echocardiogram defined as RWMA and/or wall aneurysm and/or basal septum thinning and/or LVEF <40 %. **b** Suggested algorithm for the investigation of patients with unexplained Mobitz II or third-degree AV block who are younger than 60 years. *Asterisk* (*) indicates voltage-guided or advanced imaging-guided endomyocardial biopsy (reproduced with permission from the author and journal: Birnie DH, Sauer WH, Bogun F et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart rhythm: the official journal of the Heart Rhythm Society 2014;11:1305–23) [25••]
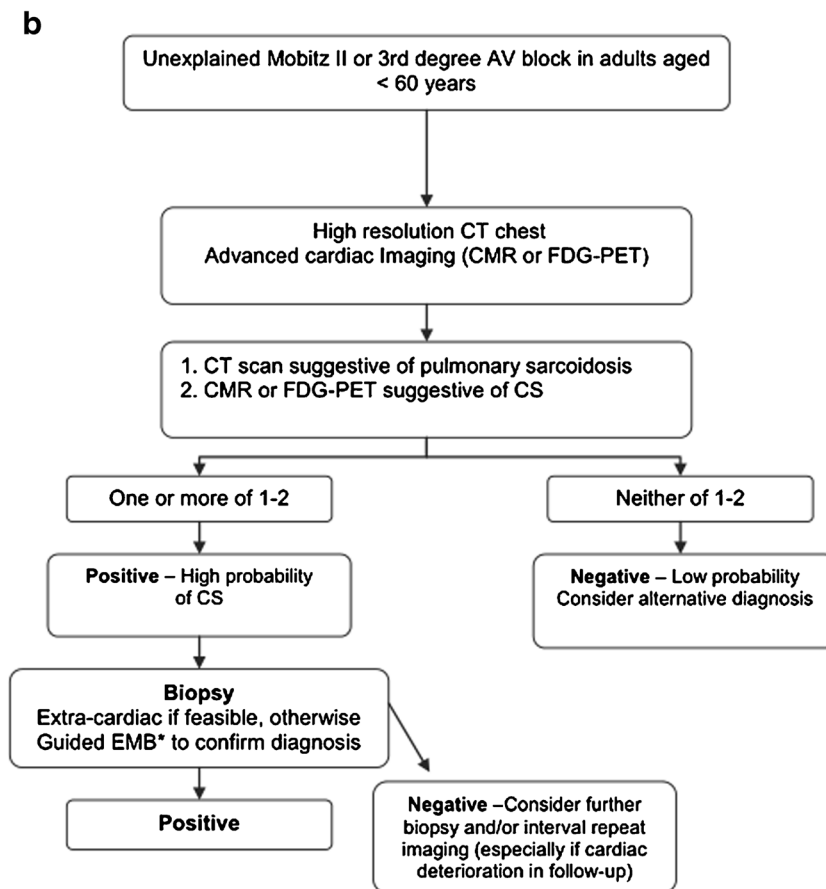
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        ┌─────────────────────────────────────────────┐
        │  Unexplained Mobitz II or 3rd degree AV block │
        │             in adults aged < 60 years         │
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        ┌─────────────────────────────────────────────┐
        │           High resolution CT chest            │
        │   Advanced cardiac Imaging (CMR or FDG-PET)    │
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        │ 1. CT scan suggestive of pulmonary sarcoidosis│
        │ 2. CMR or FDG-PET suggestive of CS            │
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One or more of 1-2	Neither of 1-2
Positive – High probability of CS	**Negative – Low probability Consider alternative diagnosis**

Biopsy
Extra-cardiac if feasible, otherwise
Guided EMB* to confirm diagnosis

Positive

Negative – Consider further biopsy and/or interval repeat imaging (especially if cardiac deterioration in follow-up)

Fig. 2 (continued)

PET-CMR to diagnose CS [79, 80]. In preliminary data in an abstract report, Wicks and colleagues have also undertaken a feasibility study of 51 patients to assess accuracy of hybrid PET-CMR for CS diagnosis [81]. They found that in isolation sensitivity of PET and CMR at detecting probable cardiac sarcoidosis was 65 and 60 % respectively; with hybrid imaging sensitivity improved to 89 % [81]. Hybrid imaging thus may enable more accurate and earlier diagnoses in this complex disease characterized by both active and chronic phases, as well as facilitate more effective monitoring of response to therapy.

Conclusions and Diagnostic Approach

Early diagnosis of CS is important because it can be associated with cardiomyopathy, atrioventricular block, ventricular arrhythmias and sudden cardiac death. Investigation for CS should be undertaken for in patients with extra-cardiac sarcoidosis and cardiac symptoms, ECG or echocardiography abnormalities (Fig. 2). Guidelines also suggest screening for CS in younger patients (≤60 years) with unexplained advanced heart block (Fig. 2) [25••]. Initial assessment should include history, examination, 12-lead ECG and echocardiogram [25••]. Echocardiography is universally available, without risk to the patient, and provides useful information about cardiac structure and function, and assesses for possible differential diagnoses.

If initial screen suggests possible CS, PET and CMR are powerful imaging tools that are preferred to other imaging modalities as they offer the best correlation with the disease [25••]. They can aid in the diagnosis of CS, and also monitor disease activity and response to treatment. CMR has the advantage of wider availability than PET, absence of radiation and is able to better detect small areas of scar and subclinical disease. PET is more sensitive and better for assessing acute inflammatory phase of the disease. It also has the advantage of being able to assess the response to anti-inflammatory therapy even in those with cardiac devices. If neither CMR nor PET is available, then investigation with Tl-201 or Tc-99m-based MPI and Ga-67 scintigraphy would be appropriate.

Surveillance imaging can assist in monitoring sarcoidosis activity, progression and response to therapy. There are no guidelines with regard to the timing of follow-up scans or how to adjust therapy after scanning. However, a reasonable approach may be repeat imaging 3–6 months after initiation of anti-inflammatory therapy. Collaborative multicentre studies are required to answer much about this condition. This

includes identifying those at risk for cardiac events, the role of ICDs, steroids and other immunosuppressive therapies, the duration of treatments and the role of advanced cardiac imaging in monitoring response to treatment.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

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