Accurate diagnosis of cardiac sarcoidosis needs a multidisciplinary approach

The optimal management of sarcoidosis requires that a clear distinction is made between the treatment of dangerous disease (i.e. major organ involvement with a risk of irreversible disability) and treatment to address unacceptable loss of quality of life (Wells et al, 2012). Cardiac sarcoidosis may be associated with a high morbidity and mortality, so accurate and timely diagnosis is particularly important. The two case reports published in this issue highlight the reality of everyday clinical practice where the diagnosis of cardiac sarcoidosis may be difficult.

Interestingly, cardiac sarcoidosis was confirmed 3 and 6 years respectively after the initial disease presentation. Baseline diagnostic tests such as electrocardiogram and echocardiography failed to provide an accurate early diagnosis in both cases, resulting in adverse outcomes: hospitalizations for arrhythmias and decompensated heart failure in the case described by Pal et al (p. 656, doi: 10.12968/hmed.2016.77.11.656) and a significant decline in left ventricular ejection fraction in the case reported by Kim et al (p. 658, doi: 10.12968/hmed.2016.77.11.658). These cases illustrate the limitations of baseline routine tests in the identification of cardiac sarcoidosis, underlining the need for a proactive multidisciplinary approach both at presentation and during subsequent follow up.

There is no 'gold standard' test for cardiac sarcoidosis, given the low sensitivity and invasive nature of an endomyocardial biopsy.

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The diagnosis is usually based on the results of non-invasive cardiac imaging modalities prompted by symptoms in a patient with biopsy-proven extra-cardiac sarcoidosis.

The widely applied Japanese Ministry of Health and Welfare criteria, based on a combination of electrical and functional abnormalities, fail both patients and clinicians (Tsuda et al, 2006). These criteria are built around the detection of clinically overt cardiac sarcoidosis, identified in 5–10% of cases, but are unequal to the detection of subclinical myocardial involvement, present in 20–30% of sarcoidosis patients at autopsy (Perry and Vuitch, 1995).

The importance of imaging

What can be done about this? The lack of emphasis on cardiac magnetic resonance imaging and the non-inclusion of positron emission tomography are major omissions in the Japanese criteria. In the last two decades, the advanced imaging modalities (cardiac magnetic resonance and positron emission tomography) have shown superiority, identifying myocardial involvement with a prevalence similar to post-mortem studies (Patel et al, 2009; Greulich et al, 2013; Birnie et al, 2014; Blankstein et al, 2014), leading to their inclusion as diagnostic criteria in the expert consensus statement from the Heart Rhythm Society.

The diagnostic superiority of cardiac magnetic resonance lies in its ability to identify subtle myocardial fibrosis, which may not necessarily cause any electrical or functional abnormalities detected by conventional investigations. Although there is no particular pathognomonic pattern of late gadolinium enhancement, focal enhanced areas in a non-coronary artery distribution may be strongly suggestive (Patel et al, 2009; Greulich et al, 2013).

The interpretation of cardiac magnetic resonance requires specific expertise in conjunction with clinical information, highlighting the importance of a multidisciplinary approach. Pal et al described patchy mid-wall fibrosis in the context of biopsy-proven sarcoidosis presenting with supraventricular and ventricular arrhythmias. This pattern in isolation could not exclude the diagnosis of an atypical hypertrophic cardiomyopathy.

Similar advances in radionuclide imaging of patients with cardiac sarcoidosis have resulted in the early identification of myocardial inflammation with a degree of high sensitivity, even before structural changes are apparent. Positron emission tomography is considered superior to gallium-67 scintigraphy and provides measurements of activity that are helpful in diagnosis, risk stratification and monitoring therapy in patients with cardiac sarcoidosis (Okumura et al, 2004). Kim et al emphasized the importance of positron emission tomography for the diagnosis despite the lack of histological confirmation.

The presence of non-magnetic resonance compatible devices has increased the use of positron emission tomography, when most often myocardial inflammation is detected among areas of fibrosis. However, the absence of positron emission tomography signal does not exclude cardiac sarcoidosis.

In clinical practice, neither test can yet be viewed as a reference standard. It is essential that cardiac magnetic resonance and positron emission tomography data are integrated with clinical information when the diagnosis is challenging. The use of resources to achieve the early diagnosis of cardiac sarcoidosis requires rigorous rationalization. It can now be argued that a multidisciplinary approach, recommended by expert groups, is mandatory (Kouranos et al, 2015a). However, there are major practical difficulties including the prevalence of sarcoidosis, the learning curve in the accumulation of multidisciplinary expertise in this field and the need to integrate modalities which are not always readily available outside expert centres.

It is difficult to escape the conclusion that a two-tier approach is required, with the creation of a handful of national centres expert in cardiac sarcoidosis and a focus on easily performed tests that serve as a trigger

for early referral. Much work remains to be done regarding this but without this approach it is likely that cardiac sarcoidosis will continue to be diagnosed 'when the train has already left the station'.

The authors propose that cardiac positron emission tomography should be considered in patients with cardiac magnetic resonance evidence of cardiac involvement, as additional information regarding disease activity helps guide therapeutic intervention (Kouranos et al, 2015b). In the case by Kim et al the information would be considered under a multidisciplinary approach allowing for accurate and consistent diagnosis and management plan.

In the case presented by Pal et al immunosuppressive treatment was introduced following the identification of late gadolinium enhancement on cardiac magnetic resonance. However, no signs of myocardial inflammatory activity were clearly identified. A cardiac positron emission tomography scan may identify ongoing active inflammation and thus potentially detect reversible stages of cardiac sarcoidosis. This probably explains the fact that a number of studies in patients with cardiac sarcoidosis presenting with ventricular tachycardia or heart failure have failed to demonstrate any clear benefit of immunosuppressive therapy (Winters et al, 1991; Sadek et al, 2013).

Treatment options

Treatment in cardiac sarcoidosis has been complicated by conflicting evidence of therapeutic benefit. However, the available evidence from randomized controlled data is limited because of the relative rarity of the condition. Previous studies have shown that intensive treatment algorithms centred on the presence of ventricular arrhythmias and heart failure may not provide any significant benefit. On the other hand, a systematic review has shown recovery of conduction abnormalities with corticosteroid treatment (Sadek et al, 2013). Immunomodulation seemed to be beneficial in both cases presented.

Accumulated clinical experience in expert centres suggests that a vigorous treatment approach earlier in the disease course improves outcomes. Although high dose corticosteroid therapy is first-line treatment, the historical view that further increases are required in the absence of clear clinical benefit is now widely questioned. Early recourse to a second-line agent is increasingly regarded as the standard of care. The use of advanced imaging modalities has been particularly helpful in rationalizing treatment. Prominent signal indicative of cardiac inflammation on cardiac magnetic resonance or positron emission tomography suggests that there is a high likelihood of major reversibility with immunomodulation. The information derived from the above tests may be useful to decide the appropriate moment for introduction of a second-line agent. In addition, as clearly presented in the case by Kim et al, evidence of steroid responsiveness should be evaluated such as the response in the left ventricular ejection fraction. Such information may justify a less aggressive regimen in the longer term. Above all, it is essential that treatments be used in cardiac sarcoidosis to prevent progression of irreversible disease.

In cardiac sarcoidosis, treatment decisions should ideally be multidisciplinary. Although yet to be evaluated in controlled studies, immunosuppressive treatment has been associated with regression of metabolic activity on cardiac magnetic resonance and cardiac positron emission tomography. The optimal use of immunosuppressive therapy is a matter of guesswork in the absence of information provided by advanced imaging modalities. The identification of patients at high risk of sudden cardiac death (either as a result of ventricular arrhythmias or complete heart block) is an essential part of the assessment of patients with cardiac sarcoidosis, as an implantable cardiac defibrillator may be required.

Expertise in the treatment of heart failure is indispensable. The integration of sarcoidosis-specific treatments, heart failure therapies and the accurate management of dangerous arrhythmias, based on advanced imaging data, cannot realistically be undertaken without a multidisciplinary approach, performed at expert centres. **BJHM**

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KEY POINTS

- An accurate and timely diagnosis is particularly important in cardiac sarcoidosis although the reality of everyday clinical practice means that this may be difficult.
- A multidisciplinary approach is required to identify cardiac sarcoidosis, with the integration of cardiac symptoms, electrocardiographic and echocardiographic abnormalities, and advanced imaging findings.
- Advanced imaging techniques may be helpful in detecting subclinical disease underdiagnosed in the past and exploring algorithms to identify patients at future risk of life-threatening cardiac complications.
- Treatment decisions in cardiac sarcoidosis should ideally be multidisciplinary. This may involve both immunomodulation and treatment of the consequences of irreversible cardiac disease, including antiarrhythmic therapy, device implantation and heart failure treatment.

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