Search for key manifestations to predict inflammation on cardiac PET in suspected cardiac sarcoidosis population

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Sarcoidosis, a multisystem granulomatous disorder, remains an enigma—the exact cause, ideal diagnostic method and a definite management are all unclear. Clarity is about the manifestations. The search for key clinical factors to predict disease has been the goal of various investigators. The diagnosis of cardiac sarcoidosis remains a challenging task for clinicians in the absence of a gold standard diagnostic tool. The diagnostic yield of endomyocardial biopsy is rather low[1] and moreover the procedure carries significant risk for patients outside expert centers. The heterogeneous nature of the myocardial granulomatous infiltration is often the main cause of diagnostic failure of such procedure.[2] Endomyocardial biopsies are often obtained from the RV free wall and apex of the atrioventricular (A-V) septum, but cardiac sarcoidosis may usually involve the basal part of the septum and the lateral wall, areas that are rarely biopsied. As a result, advanced non-invasive imaging modalities are relied upon to reach a clinical working diagnosis of cardiac sarcoidosis.

The formerly used Japanese Ministry of Health and Welfare (JMHW) criteria had focused on the identification of clinically overt cardiac sarcoidosis. They included left ventricular systolic impairment and A-V block as the major diagnostic criteria, while late gadolinium enhancement on cardiac MRI was considered minor criterion and FDG uptake on cardiac PET was not included.[3] However, the increasing use of advanced imaging modalities (cardiac MRI and cardiac PET) for the diagnosis of cardiac sarcoidosis has revealed a significant amount of patients with sub-clinical disease that previously failed to be diagnosed with conventional diagnostic modalities.[4–7] On reflection, the Heart Rhythm Society (HRS) in association with the World Association of Sarcoidosis and Other Granulomatous Diseases (WASOG) published an expert consensus statement, where abnormalities in advanced imaging modalities were considered as major diagnostic criteria in patients with extra-cardiac biopsy-proven sarcoidosis.[8] The use of the HRS criteria managed to capture a prevalence of cardiac sarcoidosis similar to autopsy studies even in the general sarcoidosis population.[6,9] However, these criteria await validation given the absence of gold standard diagnostic tool.

HRS consensus statement recommended the performance of advanced imaging (cardiac MRI and/or cardiac PET) if clinical suspicion of cardiac sarcoidosis was raised. Extra-cardiac biopsy-proven sarcoidosis patients with cardiac symptoms, electrocardiographic (ECG), or echocardiographic abnormalities were indicated as suspicious cohort of patients. In addition, all patients aged less than 60 years with second or higher degree of A-V block were considered suspected cardiac sarcoidosis patients. In the study by Tuominen et al., 137 patients were considered suspected of cardiac sarcoidosis and underwent cardiac PET. Patients presenting with unexplained syncope, A-V block, ventricular or supraventricular arrhythmias, and unexplained cardiomyopathic process on echocardiogram were included as suspected cardiac sarcoidosis patients. It would be argued as to whether this specific cohort should be considered as genuine suspected cardiac sarcoidosis

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patients. However, despite the apparent differences with the recommended cohorts of suspected cardiac sarcoidosis patients in the HRS consensus statement, this cohort clearly illustrates diagnostic difficulties that are often present in everyday clinical practice.[8]

For example, patients with unexplained syncope have been of particular interest recently. In 50% of patients with unexplained syncope, an arrhythmia was detected in a large study using continuous record of the heart rhythm with implantable loop recorders.[10] In the group of patients with bifascicular block and unexplained syncope, permanent cardiac pacing was required to prevent further episodes suggesting that further interventions may be needed in this specific group of patients.[11] The study by Tuominen et al is the first study to evaluate a screening approach of patients with unexplained syncope or other cardiac abnormalities with cardiac PET. Interestingly 24% of these patients were found to have myocardial FDG uptake indicative of active inflammation. Follow-up for cardiac outcomes and a cost-effectiveness analysis would empower the use of cardiac PET in this specific population as a screening tool.

In the same study, isolated cardiac sarcoidosis was considered a possible working diagnosis in almost half of the patients. This new entity has been increasingly considered as a working diagnosis in patients with histological evidence of granulomatous inflammation in the heart in isolation or evidence of inflammatory cardiac involvement in advanced imaging modalities without findings of any other organ involvement.[12,13] Patients with cardiac sarcoidosis may present with unexplained arrhythmic or functional abnormalities and no previous history of sarcoidosis as their initial manifestation.[14] The interpretation of positive cardiac PET in the absence of extra-cardiac sarcoidosis can be challenging. In a large cohort of cardiac sarcoidosis patients with 60% histological confirmation of the diagnosis, isolated cardiac sarcoidosis was identified in 65% of the population at presentation.[15] In another study comparing necropsy findings of patients with and without known extra-cardiac sarcoidosis that died suddenly, 40% of patients had isolated cardiac sarcoidosis.[16] However, there is no available study confirming the site of myocardial inflammation on cardiac PET with histopathological correlation. In addition, cardiac MRI and cardiac PET have not been used yet as screening tools in the general population. Finally, the behavior of isolated cardiac sarcoidosis in comparison to multi-systemic cardiac sarcoidosis is yet to be evaluated. The data for significant clinical response of isolated cardiac sarcoidosis patients on sarcoidosis-specific management remain elusive.

The increasing use of advanced cardiac imaging modalities is likely to capture a wider variety of cardiac inflammatory pathologies and in effect uncover a new field of inflammatory cardiomyopathies that may pose a diagnostic challenge in the absence of histopathological evidence. On one hand, these modalities have demonstrated diagnostic superiority based on their ability to identify myocardial fibrosis and evidence of active myocardial inflammation, which may not necessarily cause any electrical or functional abnormalities and is therefore not detected by conventional investigations. Although there is no particular pathognomonic pattern of late gadolinium enhancement on cardiac MRI, focal areas of enhancement that are in a non-coronary artery distribution may be suggestive of cardiac sarcoidosis.[4–6,8] Cardiac PET is considered superior to the traditionally used gallium-67 scintigraphy and provides measurements of activity that are helpful in the diagnosis, risk stratification, and the monitoring of therapy in patients with cardiac and systemic sarcoidosis.[7,8] The presence of non-MRI compatible devices has increased the use of PET in the diagnosis of cardiac sarcoidosis, when most often myocardial inflammation is detected among areas of fibrosis and a mismatch perfusion metabolism pattern is identified. However, the absence of extra-cardiac (biopsy-proven or clinical) sarcoidosis would weaken the argument of cardiac sarcoidosis in these cases although an inflammatory process is highly likely when intense signal is identified. It is essential that cardiac MRI and cardiac PET data are integrated with clinical information when the diagnosis is challenging. A multidisciplinary approach, recommended by expert groups, seems mandatory in this case acknowledging the practical difficulties regarding the accumulation of multidisciplinary expertise in the field and the availability of the advanced imaging modalities outside expert centers.

In the study by Tuominen et al patterns are classified on cardiac PET as focal, focal-on-diffuse, global-diffuse, and diffuse-non-global. The focal and focal-on-diffuse patterns were considered suggestive of active cardiac sarcoidosis. Although patterns of patchy infiltration on dedicated cardiac PET were considered as diagnostic criterion of cardiac sarcoidosis in HRS consensus statement, specific patterns for cardiac sarcoidosis have not been confirmed.[8] Several descriptions have been used for the description of the FDG uptake but none have been validated with histopathological findings or outcome measures so far.[7,17–20] Skali et al recommended that all patients undergoing cardiac PET should also undergo myocardial perfusion scan with locally available tracers such as technetium, thallium, rubidium, or ammonia.[21] The absence of cardiac FDG uptake (following adequate metabolic preparation) does not exclude cardiac sarcoidosis, and myocardial perfusion scans may identify fibrotic areas compatible with cardiac sarcoidosis in the absence of inflammatory activity. The integration of both perfusion and metabolism would provide the ability to

identify patterns that correlate the presence of disease and disease activity with mismatch perfusion/metabolism pattern being more often seen in cardiac sarcoidosis, as well as exclude the possibility of overlapping ischemic heart disease. Since endomyocardial biopsies are mostly performed on RV, the yield from biopsies is likely to be higher in patients with abnormal RV-uptake as shown by Tuominen et al.

Tuominen et al showed strong correlation between active cardiac sarcoidosis and female sex as well as advanced A-V block. Age, gender, and race have been identified as factors associated with different sarcoidosis manifestations but gender was never found to predict cardiac involvement.[22] A recent study in 1375 consecutive sarcoidosis patients in Poland found that cardiac sarcoidosis is more common in men than women but did not integrate in the analysis of the evidence of active disease obtained from cardiac PET.[23] On the other hand, a Japanese study showed higher prevalence of cardiac sarcoidosis in women and other studies failed to identify any gender difference in prevalence.[24] These differences may highlight the genetic background of the disease, which may relate to geographical variation. However, it is hardly fathomable that gender would guide the performance of cardiac PET in patients with symptoms or other cardiac abnormalities.

A-V block is the most common presentation of clinically overt cardiac sarcoidosis.[8] Direct granulomatous infiltration or fibrosis of the basal septum or the nodal artery is considered the underlying pathophysiological mechanism. Therefore, advanced A-V block is acknowledged as a stand alone diagnostic criterion in the both the JMHW and HRS criteria set.[3,8] New onset advanced A-V block has been associated with intense FDG uptake in two studies indicating that it may well represent a marker of disease activity.[14,18] When outcomes in patients with advanced A-V block as the initial disease manifestation were evaluated, those patients had a high rate of fatal cardiac events.[25] Therefore, an indication for implantable cardioverter-defibrillator has been considered as recommendation IIa in HRS consensus statement.[8] The above findings would suggest that new onset advanced A-V block would most likely be related with active cardiac sarcoidosis, and a cardiac PET is required for confirmation and monitoring of the disease. The integration of biomarkers in the diagnosis of cardiac sarcoidosis remains unknown. Plasma NT-proBNP and high sensitivity troponin levels have been considered as a biomarker in the assessment of cardiac involvement, but it is also found elevated in patients with sarcoidosis and pulmonary hypertension.[26–28] Whether such biomarkers could be integrated with the clinical information to identify patients that would benefit undergoing advanced cardiac imaging remains to be evaluated in larger studies.

In conclusion, cardiac sarcoidosis may be associated with high morbidity and mortality and therefore an accurate and timely diagnosis is of particular importance. In the absence of gold standard diagnostic test, the diagnosis relies on non-invasive cardiac imaging modalities. Cardiac PET is very useful in identifying both the presence of disease and especially the disease activity. The role of PET in identifying cardiac inflammation earlier than MRI is of interest. However currently, neither cardiac MRI nor cardiac PET can be viewed as a gold standard tool for diagnosis of cardiac sarcoidosis in everyday clinical practice. It is essential that CMR and PET findings be integrated with clinical information to reach a consensus diagnosis until we solve the enigma of sarcoidosis.

Disclosure

The authors have indicated that they have no financial conflict of interest.

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