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REVIEW ARTICLE−DISEASE DISCOVERED IN JAPAN AND THE ROLE OF NUCLEAR CARDIOLOGY

Problems of Cardiac Sarcoidosis to Be Solved: Considering Clinical Guidelines

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Abstract

Cardiac sarcoidosis has long been an ambiguous diagnosis and tended to be misdiagnosed because of the low sensitivity of endomyocardial biopsy. In addition, cardiac sarcoidosis sometimes mimics other diseases, such as dilated cardiomyopathy and myocardial infarction with aneurysm. Recent advancements in imaging make it possible to detect it earlier, differentiate from other diseases, and monitor the treatments. New guidelines for cardiac sarcoidosis appreciate imaging and include isolated cardiac sarcoidosis. Therefore, detection rate has been increasing after introduction of the new guidelines. However, problems still remain, such as optimal doses of steroids, alternative therapy to steroids, and complicated diagnostic criterion. This review focuses on the remaining problems to be solved regarding cardiac sarcoidosis management.

Keywords: Cardiac sarcoidosis, Diagnosis, FDG, Guidelines, PET
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Sarcoidosis is a systemic inflammatory disorder of unknown etiology affecting people of any age. Middle age women tend to be affected, and it is relatively prevalent among the blacks in the US, the Scandinavians, and the Japanese. The disease is characterized by heterogeneous distribution of epithelioid granulomatous inflammation without caseous necrosis and unpredictable clinical course. Divergent phenotypes from asymptomatic status to sudden death have been identified. Multiple organs, including lungs, lymph nodes, eyes, bones, liver, spleen, skin, muscles, nervous system and heart are involved. Sarcoidosis is reported first as benign skin lesion like “psoriasis” in 1878 (1) and lately confirmed as sarcoid nodule in 1900 by necropsy (2). Although about 20% of patients are chronically progressive, its inflammation spontaneously resolves in general. Therefore, it has been believed to be benign disease. Cardiac involvement had been considered rare; however, an autopsy report demonstrated that myocardial involvement was identified as much as 50% of sarcoidosis cases (3) and about 80% of deaths are attributed to Cardiac sarcoidosis (CS) in Japan (4). The most common causes of death are fatal ventricular arrhythmias and heart failure. Therefore, early detection and treatment of cardiac sarcoidosis are crucial.

Diagnosis of CS has been made based on the guidelines issued in 1992 by the Japanese Ministry of Health, Labour and Welfare. Then, the guideline was revised in 2006. The revised guideline requires histologically proved sarcoid tissue from the heart (Histologic diagnosis group) or other than the heart with evidence of clinical findings which is strongly suggestive of cardiac involvement (Clinical diagnosis group). However, sensitivity of endomyocarial biopsy is very low. Therefore, the clinical diagnosis group is much prevalent in the clinical practice. In the clinical diagnosis group, the role of imaging has become essential. As diagnostic imaging has progressed, new guidelines for the diagnosis and treatment of CS has been expected. Recently, the integrated guidelines has been published from joint committee of the Japanese Circulation Society, the Japanese College of Cardiology, the Japanese Heart Failure Society, the Japan Society of Sarcoidosis and other Granulomatous Disorders, the Japanese Society of Nuclear Cardiology, and the Japanese Heart Rhythm Society in 2016 (5). This guideline unified the diagnostic criteria for

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the diagnosis of CS. Isolated CS is firstly defined. Therefore, clarifying the pathophysiology and progress of treatment are expected. Some problems still remained to be solved, including judgement of treatment efficacy, lack of randomized controlled trial, dose and duration of steroid therapy, and management of isolated CS.

The role of imaging

The diagnosis of CS has relied on histology as the gold standard; however, the detectability of endomyocardial biopsy is as low as 20% (6) because inflammation usually locates in the mid/outer layers rather than endocardial layer of myocardium with patchy distribution (7). In addition, CS is difficult to distinguish from some other diseases, such as dilated cardiomyopathy, and myocardial infarction with aneurysm. Recently, advancement of cardiac imaging, including cardiac magnetic resonance imaging (MRI), ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET), and echocardiography has been made. Cardiac MRI has high spatial resolution and can be performed without ionized radiation. Late-gadolinium enhancement (LGE) can detect fibrosis which is consistent with pathology in CS. Therefore, cardiac MRI can detect sarcoid lesion not only horizontal direction but vertical one. LGE can be detected about 80% of CS cases (8). However, gadolinium is harmful for patients with chronic kidney disease; thus it should be avoided for those population. In such cases, T2-weighted STIR sequence is useful in detecting edematous tissue. In addition, T1-mapping technique allows us to estimate extracellular fluid volume which reflects edematous tissue due to active inflammation that could be reversible with steroids/immunosuppressive therapy. Therefore, edematous tissue on MRI may be able to utilize for monitoring therapy. Cardiac MRI has high diagnostic yields with sensitivities 75-100% and specificities 77-78% (9). ^{18}F-FDG PET detects active inflammation as a hot spot in CS. Traditionally, ^{67}Ga-citrate scintigraphy has been used to detect active inflammation; however, ^{67}Ga-citrate scintigraphy is much less sensitive than ^{18}F-FDG PET for mild to moderate active inflammation. In addition, lower spatial resolution is another negative aspect. ^{18}F-FDG PET has good spatial resolution and is very sensitive (nearly 100%) in the detection of active sarcoidosis (9). Therefore, ^{18}F-FDG PET has replaced the role of ^{67}Ga-citrate scintigraphy in the new guideline. ^{18}F-FDG PET is so sensitive to detect active inflammation that it can be used for monitoring the treatment (Fig. 1). However, there is controversy with preparation for ^{18}F-FDG PET. To obtain appropriate ^{18}F-FDG PET images, physiological glucose uptake by myocardium must be suppressed so that ^{18}F-FDG uptake rigorously reflects glucose uptake by macrophages due to active inflammation. Low-carbohydrate/high-fat diet and elevated free fatty acid levels induced by unfractionated heparin administration may also be useful to suppress physiological glucose uptake. How long is enough to suppress physiological glucose uptake by myocardium? Is heparin administration necessary? The latest recommendation by the Japanese Society of Nuclear Cardiology indicates more than 18 hours fasting without heparin administration (10). Echocardiography reveals basal interventricular septal thinning and regional myocardial abnormalities, such as aneurysm and focal thickening with CS. Systolic and diastolic dysfunction, abnormal wall motion, and pericardial effusions are also considered as findings of CS. These findings have been reported in 4-55% of patients with extra CS and 77% of patients with known CS and are less specific findings (9).

As a whole, recent advancement of cardiac imaging improves diagnostic yields of CS. Especially, combination of ^{18}F-FDG PET and MRI with LGE increases specificity and may be the most powerful diagnostic tool so far. Image-guided treatment by ^{18}F-FDG PET is one of the targets for investigation in the future.

Problems to be solved

First of all, diagnostic criteria is so complicated that diagnosis of CS may be confusing. For example, clinical diagnosis group requires that more than 2 organs out of respiratory system, eyes, and heart are involved with more than 2 features present out of 1) bi-hilar lymphadenopathy, 2) elevated serum angiotensin converting enzyme activity or lysozyme value, 3) elevated serum soluble interleukin-2 receptor value, 4) apparent accumulation of ^{67}Ga-citrate or ^{18}F-FDG, and 5) significant lymphocytosis in bronchoalveolar lavage with CD4/CD8 $>$ 3.5 in the absence of histological evidence of CS. Cardiac involvement is defined that 1) more than 2 main features or 2) 1 main feature with more than 2 sub features present. Main features consist of a) advanced atrioventricular block or fatal ventricular arrhythmias, b) thinning of basal interventricular septum or morphological abnormality of ventricular wall, such as aneurysm, thinning other than septum, and focal thickening, c) left ventricular systolic dysfunction (LVEF $<$ 50%) or regional wall motion abnormalities, d) Abnormal accumulation of ^{67}Ga-citrate or ^{18}F-FDG, and e) delayed enhancement of gadolinium with magnetic resonance imaging. Sub features consist of f) ECG abnormalities including ventricular arrhythmias, bundle branch blocks, axis deviations, and abnormal Q waves, g) focal defects on myocardial perfusion scintigraphy, and h) mononuclear cell infiltration with more than intermediate fibrosis of myocardium by endomyocardial biopsy.

There is another struggle with insurance reimbursement system in Japan. The cost of ^{18}F-FDG PET is covered by insurance not for diagnosis but for identification of inflamma-

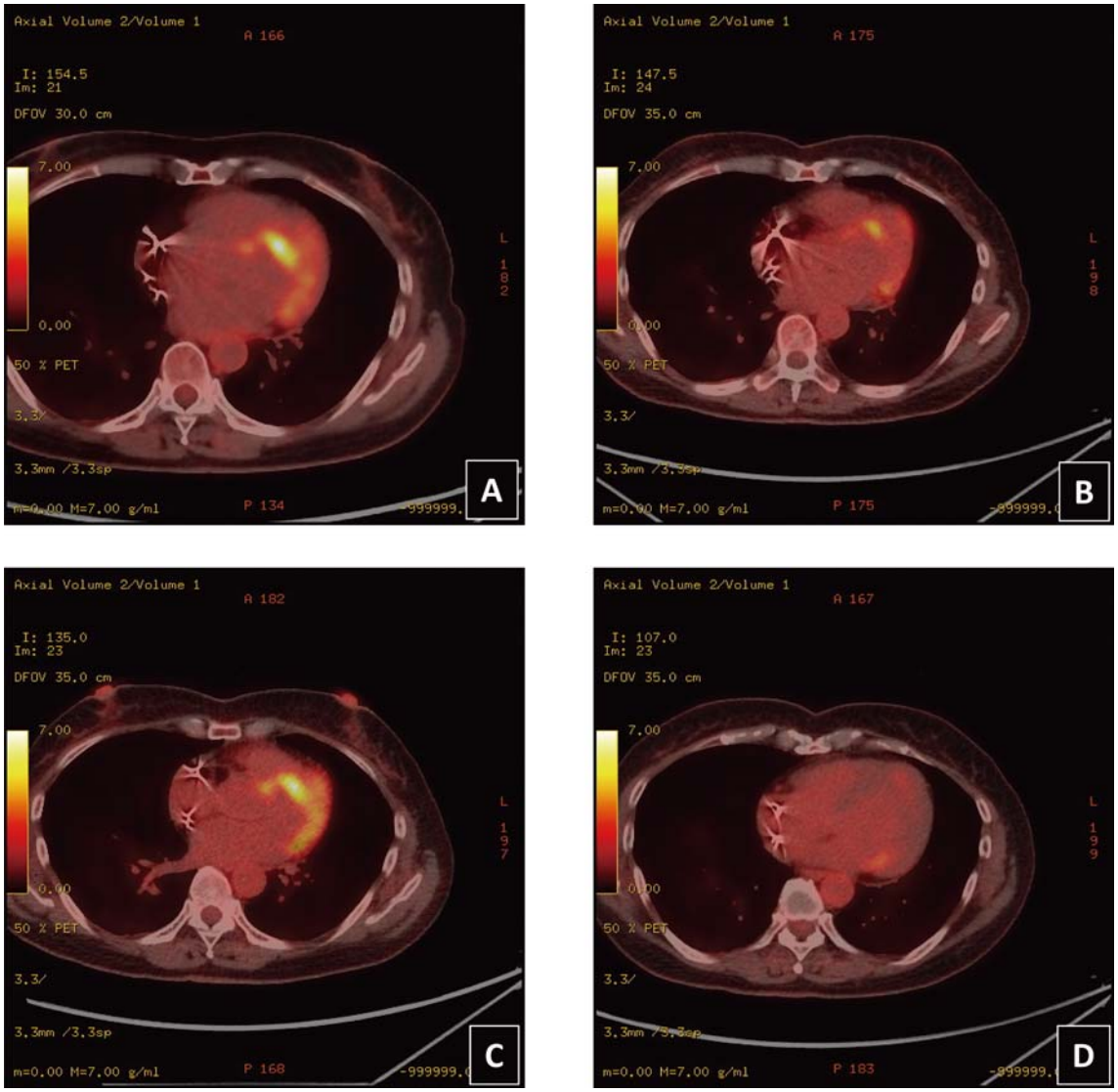

Fig. 1 Serial ^{18}F-FDG PET/CT imaging of active cardiac sarcoidosis.
A: Active inflammation was detected (SUVmax 7.40) before treatment. **B**: Predonisolone (60mg/every other day) supresses the inflammation (SUVmax 5.56). **C**: Inflammation reactivated after tapering of predonisolone (30mg/every other day). **D**: Inflammation has been under control (SUVmax 3.22) after methotrexate added (predonisolone 10mg/day + methotrexate 7.5mg/week).

tion site of CS. Therefore, establishment of cardiac sarcoidosis is prerequisite for ^{18}F-FDG PET under present insurance system in Japan.

Second, isolated CS prevalence is much higher than that has been reported in the past. Isolated CS occupies 20-50% of all sarcoidosis cases (8, 11). Therefore, the new guideline defined isolated CS as a new entity, consisting of histological diagnosis group and clinical diagnosis group. Clinical diagnosis group must fulfill 4 main features, including d) abnormal accumulation of ^{67}Ga-citrate or ^{18}F-FDG indicated above (5). This guideline probably facilitates diagnosis of CS in patients suspected having CS but previously unrecognized.

Third, some prognostic reports indicate that isolated CS, low ejection fraction, perfusion defects, positive ^{18}F-FDG PET, and no steroid therapy predict poor outcomes (4, 8, 12); however, there is no randomized controlled trials. This fact leads to lack of Ib or upper level of evidence in the guidelines.

Fourth, there is no consensus regarding judging effectiveness of treatment. T2-weighted STIR sequence or T1-mapping on MRI may be useful in assessing active inflammation by qualitative and quantitative evaluation of edematous tissue. ^{18}F-FDG PET may be most promising test assessing activity of inflammation. Standardized uptake value (SUV) can be used for quantification of inflammation activity; however, optimal cut-off value discriminating active from inactive state is not determined.

Fifth, optimal initial and/or maintenance dose of steroids are not determined. In addition, alternative therapies to steroids are also not determined. Possible agents include methotrexate, azathioprine, infliximab, cyclophosphamide, and cyclosporine

are recommended; however, only case reports and small studies endorsed effectiveness.

Perspectives

The new guidelines for cardiac sarcoidosis may facilitate diagnosis and treatment. However, the etiology is not clear. It is difficult to prove histological evidence. Although detectability of endomyocardial biopsy is very low, image-guided biopsy using ^{18}F-FDG PET and MRI may improve the sensitivity, especially for patients with positive ^{18}F-FDG PET and transmural LGE on MRI (13, 14). It is not determined the optimal timing and strategy of treatment. Therefore, it has not solved the problems of diagnosis and treatment of CS yet but it is beginning to solve the remaining problems.

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Conflicts of interest

None.

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