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Editorial

Editorial: Diagnosis of cardiac sarcoidosis – What is the role of endomyocardial biopsy?

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In the present case report [1], Moriyama et al. reported a case of adult-onset of Kawasaki disease and cardiac sarcoidosis. They clinically diagnosed their case as cardiac sarcoidosis using various imaging modalities, not based on histopathological confirmation by biopsy from an extracardiac organ or by endomyocardial biopsy. The definitive diagnostic test for cardiac sarcoidosis is endomyocardial biopsy; however, the sensitivity of endomyocardial biopsy is low, which makes it sometimes difficult to diagnose suspected cases for cardiac sarcoidosis.

While the lungs and thoracic lymph nodes are most commonly involved in sarcoidosis, myocardial involvement occurs in 20–30% of patients, although only 5% may be diagnosed antemortem [2]. Isolated cardiac sarcoidosis can also present in the absence of clinically evident extracardiac involvement, although this is somewhat less common [3]. Prognosis is highly variable in cardiac sarcoidosis, with 5-year survival rates ranging from 60 to 90%, which is related to extent and sites of cardiac involvement [4]. Most deaths due to cardiac sarcoidosis are due to ventricular arrhythmia or atrioventricular block, and progressive heart failure due to massive granulomatous and/or fibrosis infiltration of the myocardium. Given the potential mortality associated with cardiac sarcoidosis, early diagnosis associated with prompt therapy is critical and may be lifesaving.

The diagnosis of cardiac sarcoidosis should be considered in two clinical scenarios: (i) in patients with extracardiac biopsy-proven sarcoidosis, with or without cardiac symptoms; and (ii) in patients with no previous histological diagnosis of sarcoidosis but with unexplained cardiomyopathy, atrioventricular block, or ventricular arrhythmia [2]. Cardiac involvement in sarcoidosis is particularly difficult to diagnose because the manifestations are nonspecific, and the sensitivity and specificity of diagnostic modalities are limited.

The international expert consensus statement released by the Heart Rhythm Society in 2014 recommended the use of cardiac history, 12-lead electrocardiography (ECG), and echocardiography for screening of patients with biopsy-proven extracardiac sarcoidosis for possible cardiac sarcoidosis [5]. Abnormalities on ECG, such as complete left or right bundle branch block, pathologic Q waves, second-degree or third-degree atrioventricular block, sustained or nonsustained ventricular tachycardia, have been noted in 20–31% of sarcoidosis patients [6].

Echocardiographic findings are often nonspecific, but the presence of echocardiographic abnormalities in patients with known extracardiac sarcoidosis should strongly suggest cardiac sarcoidosis. Echocardiographic abnormalities are reported in 24–77% of cardiac sarcoidosis patients [7]. Some more specific findings include wall thinning of the basal anterior septum (Fig. 1), regional wall aneurysm, or motion abnormalities not in a coronary artery distribution.

Resting perfusion scintigraphy employing thallium-201 (^{201}Tl) may show areas of decreased uptake in patients with cardiac sarcoidosis. Segmental areas of decreased ^{201}Tl uptake are believed to correspond to areas of fibrosis or granulomatous replacement. Gallium-67 (^{67}Ga) accumulates in areas of active inflammation, and thus, has been employed in the detection of cardiac sarcoidosis. However, many areas of cardiac involvement are free of inflammation and consist only fibrogranulomatous scar which could not be detected by ^{67}Ga. The sensitivity of ^{67}Ga scintigraphy is 18–50%. ^{67}Ga scintigraphy could detect skin and muscle lesions that cannot be clinically detected by any other tests, often aiding in biopsy-based diagnosis (Fig. 2).

Recently, positron emission tomography (PET) and cardiac magnetic resonance (MRI) imaging techniques have replaced traditional radionuclide studies because of their superior diagnostic performance. ^{18}F-fluorodeoxyglucose PET (FDG-PET) is superior to ^{201}Tl and ^{67}Ga scanning in detecting early stages of cardiac involvement. As in the present case [1], a pattern of focal uptake (patchy with no background activity) and focal on diffuse uptake (intense patchy uptake with less intense diffuse uptake) have been considered indicative of active granulomatous myocarditis. A meta-analysis to examine the role of FDG-PET scans in cardiac sarcoidosis showed 89% (79–100%) sensitivity and 78% (38–100%) specificity [8]. FDG-PET scanning can also provide a diagnostic modality for patients unable to undergo cardiac MRI because of the presence of implantable cardiac devices or severe renal dysfunction. FDG-PET requires a strict protocol of carbohydrate restriction and prolonged fasting to force the myocardium into free fatty acid metabolism and reduce the background myocardial activity [9].

Cardiac MRI with gadolinium enhancement is increasingly becoming the technique of choice for the evaluation of cardiac sarcoidosis [7]. The presence of delayed gadolinium enhancement that is not consistent with a coronary artery distribution is

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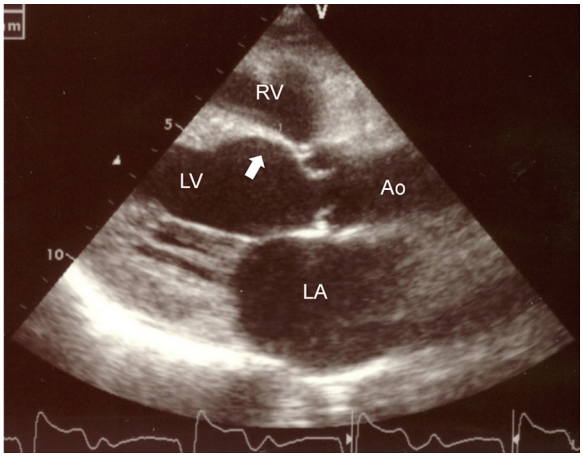

Fig. 1. Echocardiogram, parasternal of long axis view. Note the thinned segment in the basal anteroseptal wall (arrow). Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

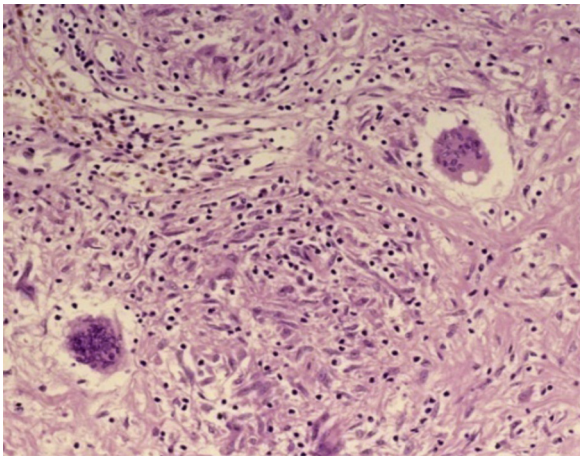

Fig. 2. ^{67}Ga scintigram showed increased uptake in the left supraclavicular lymph node, and histopathological examination of the left supraclavicular lymph node biopsy specimen showed typical non-caseating granulomas.

suggestive of cardiac sarcoidosis and scar tissue formation, which is often found in the midmyocardium and epicardium as opposed to the endocardial predominance seen in ischemic disease. However, many other patterns of gadolinium enhancement and even a pattern that is typical for prior myocardial infarction can also represent cardiac sarcoidosis. Cardiac MRI readily outperforms radionuclide imaging for the diagnosis of cardiac sarcoidosis, with a sensitivity of 76–100% and specificity of 78–92% [10].

Despite the above advanced imaging modalities, the only absolute test for organ involvement in sarcoidosis is histologic examination of tissue for the presence of non-caseating granulomas (Fig. 2). In patients with extracardiac sarcoidosis, lymph node or lung biopsy is typically targeted first due to the higher diagnostic yield and lower procedure risk. In those patients, myocardial involvement is commonly demonstrated with imaging modalities; routine endomyocardial biopsy to confirm myocardial involvement is not recommended, given the procedural risk and the characteristically low sensitivity of histologic examinations, revealing non-caseating granulomas in less than 25% of patients with cardiac sarcoidosis, as a result of the focal and patchy nature of cardiac sarcoidosis [2]. The infiltration has a predilection for the basal ventricular septum and the left ventricular free wall.

On the other hand, in situations where patients are with unexplained atrioventricular block, ventricular tachycardia, or cardiomyopathy without a prior histological diagnosis of extracardiac sarcoidosis, obtaining pathology ultimately becomes important for diagnostic confirmation. Biopsies should be performed safely on the accessible cutaneous lesions or palpable lymph nodes that appear to be affected by radiographic abnormalities (Fig. 2). In cases of negative extracardiac biopsy or isolated cardiac sarcoidosis, endomyocardial biopsy may be required to confirm the diagnosis of cardiac sarcoidosis. Biopsies can be guided by electroanatomic mapping or morphologic examinations, or performed during the left ventricular assist device (LVAD) or before cardiac transplantation [11].

In the diagnostic criteria for sarcoidosis of the Japanese Society of Sarcoidosis and Other Granulomatous Disease, histopathological examination is the mainstay of diagnosis [3]; however, the criteria do not mandate positive biopsies (either cardiac or extracardiac) for diagnosis of cardiac sarcoidosis, as was diagnosed clinically in the present case without histopathological confirmation [1].

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