Introduction

Sarcoidosis is a cryptogenic systemic granulomatous disease that primarily affects the lung parenchyma. It can also cause significant adenopathy and ophthalmic, skin, and cardiac disease [1]. The cardiac lesions associated with sarcoidosis are characterized by the non-caseating granulomas accompanied by giant cells in the endocardium, myocardium, and epicardium as well as scarring of these tissues [2-5].

While cardiac involvement may result in various clinical manifestations such as heart block, congestive heart failure, ventricular arrhythmias, and even sudden death, antemortem diagnosis is generally difficult [2-5]. The prognosis of sarcoidosis is influenced by the presence and severity of cardiac lesions [2-4]. Therefore, accurate diagnosis of heart involvement is extremely important. Echocardiography is crucial along with electrocardiography, radionuclide testing and endomyocardial biopsy for the diagnosis of cardiac sarcoidosis.

1. Conventional echocardiographic findings associated with cardiac sarcoidosis

While echocardiography does not often show abnormal findings in the early stage of cardiac sarcoidosis, the following findings can be seen with disease progression. The echocardiographic features of 46 successive patients with cardiac sarcoidosis in our institution are summarized in Figure 1.

1-1. Segmental wall thinning and wall motion abnormality

The following sites are often affected with cardiac sarcoidosis: the interventricular septum (IVS), in particular the basal portion; the basal left ventricular (LV) posterior wall; LV free wall including the papillary muscle; and the right ventricular (RV) free wall [2] (Figure 2). Thus, segmental wall thinning and wall motion abnormality were found in 39 cases (85%) in our series. However, atrial involvement is found in only a few cases [2]. The most characteristic finding is localized thinning of the basal portion of IVS [6] (Figure 3). The wall thinning involving the basal IVS was recognized in 30 cases (65%) in our series. Morimoto et al measured the thickness of IVS at the standard level (A) and that of the thinnest IVS (B) at the site 10 mm below the aortic valve, and calculated the optimal cut-off value to diagnose cardiac sarcoidosis [7]. They reported that cardiac involvement could be diagnosed with excellent specificity (99.0%) with either B ≤ 4 mm or B/A ≤ 0.6. In our series, there were 9 cases that showed regional wall thinning without basal IVS thinning, and the most common site of involvement was the infero-posterior wall.

1-2. Diffuse wall motion abnormality and reduced cardiac function

Extensive infiltration of LV myocardium can present as idiopathic dilated cardiomyopathy (DCM); in other words, severe LV enlargement and diffusely reduced wall motion (Figure 4). Twenty patients (43%) showed diffuse wall motion abnormality in our series, and their mean value of LV ejection fraction (EF) measured by...
Fig. 1. The incidence of echocardiographic features of the 46 successive patients with cardiac sarcoidosis (mean age, 62 years; 26 female) in our institution. The diagnosis of sarcoidosis was made histologically in 28 patients, and clinically in the others based on the various lesions (ocular, 10; pulmonary, 5; lymphatic, 2; and dermatologic, 1). The involvement of heart could be proven by endomyocardial biopsies in 16, and by either echocardiography or gallium-67 scintigraphy in the others. LV = left ventricular; IVS = interventricular septum; RV = right ventricular; MR = mitral regurgitation.

Fig. 2. The common sites of sarcoid cardiac involvement. a: the basal interventricular septum; b: the basal left ventricular (LV) posterior wall; c: LV free wall including the papillary muscle; d: the right ventricular (RV) free wall. RA = right atrium; LA = left atrium. Reproduced from Roberts WC, McAllister HA Jr, Ferrans VJ. Sarcoidosis of the heart. A clinico-pathologic study of 35 necropsy patients (group I) and review of 78 patients previously described necropsy patients (group II). Am J Med 1977; 63: 86-108, by permission of Elsevier ©1977.
Fig. 3. These 3 cases demonstrated the representative echocardiograms of thinned basal interventricular septum (IVS, arrow heads). The extent of this abnormal finding has a wide spectrum: from relatively small area limited in the just basal portion of IVS (a) to a wide area extending to the mid-portion (c).

Fig. 4. Echocardiograms from a 73-year-old woman who had been already diagnosed as having ocular sarcoidosis and suffered from chronic heart failure. Her echocardiograms showed diffusely reduced left ventricular wall motion. Especially, inferior wall motion was severely reduced (arrow heads). We clinically diagnosed her as having cardiac sarcoidosis despite a negative endomyocardial biopsy. A heterogeneous distribution of wall motion abnormalities have been described as a characteristic feature in cardiac sarcoidosis differently from idiopathic dilated cardiomyopathy. ED = end-diastole; ES = end-systole.
the Simpson disk method was markedly lower than that of the others (22 vs. 47%). A previous study compared 30 patients with DCM and 15 patients with cardiac sarcoidosis in terms of echocardiographic findings and wall motion abnormality as assessed by left ventriculography [8]. Among the patients with cardiac sarcoidosis, the mean value of LV diastolic diameter was 64 mm and that of fractional shortening was 16%, while among the patients with DCM, it was 68 mm and 15%, respectively. Neither of these differences was significant. However, abnormalities of LV wall thickness were significantly more common in patients with cardiac sarcoidosis than in those with DCM (73% vs. 17%). Among the patients with cardiac sarcoidosis, regional wall thinning was recognized in 6 patients, wall hypertrophy in 4, and both in 1. Nine of these 12 (75%) abnormal wall thickness were found in the IVS. In contrast, wall hypertrophy was never detected in patients with DCM. Consequently, this is an extremely important finding for differentiating cardiac sarcoidosis accompanied by reduced LV contraction from DCM. Moreover, EF was not different between the 2 groups; however, the proportions of dyskinetic and normokinetic regions in cardiac sarcoidosis were 23 and 12%, respectively, compared to 7 and 3%, respectively, in DCM. Thus, heterogeneous distribution of wall motion abnormalities characterized by the presence of dyskinetic or akinetic segments coexistent with normokinetic segments are another characteristic finding in cardiac sarcoidosis. This is thought to reflect patchy distributions of granuloma infiltrations and scar formations in the myocardium.

Some patients with severely reduced LV contraction often show ventricular dyssynchrony. In such patients, the severity and extent of dyssynchrony can be assessed using tissue Doppler imaging [9] (Figure 5). Severely reduced LV contraction also causes intraventricular thrombus formation, which was recognized in 2 of our cases during their whole clinical course [2]. Moreover, there has been a report of cardiac sarcoidosis localized in the RV [10]. In our series, 2 cases showed diffuse RV wall motion abnormality besides the basal IVS thinning. Consequently, the careful observation of RV wall motion is also necessary in patients with suspected cardiac sarcoidosis.

1-3. Ventricular aneurysm

The patients with extensive myocardial involvement occasionally develop LV aneurysm, which can cause intractable ventricular arrhythmia [11, 12]. In our series, we recognized 8 patients (17%) showing a ventricular aneurysm. The most common site was the inferior wall (Figure 6). Autopsy studies have confirmed ventricular aneurysm in 8-10% of patients who died of cardiac sarcoidosis [2]. As to myocardial fibrosis and aneurysm formation, corticosteroids that are used in the treatment of sarcoidosis could accelerate the progression of myocardial fibrosis in consequence of healing of sarcoid granuloma, which possibly complicates disease course.

Fig. 5. Myocardial tissue Doppler imaging (TDI) from a 52-year-old woman who suffered from intractable heart failure owing to cardiac sarcoidosis. Her clinical status improved by cardiac resynchronization therapy (CRT). TDI shows that the difference between the timing of the peak systolic velocities measured at the septal (blue arrow) and lateral (red arrow) walls was markedly shortened from 90 to 15 ms after CRT.
1-4. Ventricular wall hypertrophy

Some patients with cardiac sarcoidosis morphologically mimic hypertrophic cardiomyopathy (Figure 7). Yazaki and colleagues reported a patient with cardiac sarcoidosis showing asymmetric septal hypertrophy (ASH) due to localized wall hypertrophy in the basal portion of the IVS [13]. Although sarcoid granuloma was not confirmed in RV endomyocardial biopsy in this patient, corticosteroid administration regressed wall hypertrophy, thus concluding that septal hypertrophy might be a consequence of early myocardial lesions associated with sarcoidosis. Since endomyocardial biopsy confirmed inflammatory infiltrate and interstitial edema, wall hypertrophy may be related to these inflammatory changes.

In our series, 8 cases (17%) showed regional LV wall hypertrophy, which was more common than we had expected. All of them showed hypertrophy in the IVS and also regional wall thinning in other regions (Figure 8).

Similar to the above report, transient wall hypertrophy of RV free wall due to cardiac sarcoidosis also has been reported [14].

1-5. Pericardial effusion

Infiltration of the pericardium can cause pericardial effusion. Two cases (4%) showed significant pericardial effusion during their whole clinical course in our series. One of them was a very rare case who suffered from cardiac tamponade as the first clinical manifestation. A similar case has been reported before [15]. Autopsy studies have documented significant pericardial effusion in 2-8% of patients who died of cardiac sarcoidosis [2].

1-6. Valvular insufficiency

Mitral regurgitation (MR) is not uncommon in cardiac sarcoidosis. In our cases, 15 (33%) out of 46 patients showed MR greater than moderate degree (Figure 9). Twelve patients did not show any organic lesions of the mitral valve, and the others showed mitral valve prolapse. The mean value of EF and LV diastolic diameter in these 12 cases were 27% and 68 mm, respectively. In the past, the papillary muscle dysfunction due to sarcoid involvement had been believed to cause MR [2]. However, functional MR may be one of the important causes of MR accompanied by LV systolic dysfunction and dilation owing to cardiac sarcoidosis [16, 17]. Sarcoidosis can be accompanied by hypercalcemia; occasionally this takes the form of severe mitral annular calcification, which may also cause MR [2].
Fig. 7. An echocardiogram from a 72-year-old woman who had been histologically diagnosed as having subcutaneous sarcoidosis. She required permanent pacing because of complete atrioventricular block. The clinical course strongly suggested cardiac involvement of sarcoidosis, and her echocardiogram showed regional hypertrophy of the interventricular septum (arrow heads).

Fig. 8. An echocardiogram from a 68-year-old man who suffered from ventricular tachycardia. He was histologically diagnosed as sarcoidosis by lymph node biopsy. His echocardiogram showed localized thinning of the basal interventricular septum (IVS, closed arrow head) accompanied with hypertrophied adjacent IVS (arrows). The posterior wall also revealed regional thinning (open arrow heads).

Fig. 9. Echocardiograms from a 55-year-old woman requiring combined cardiac resynchronization therapy and implantable cardioversion defibrillation (CRT-D) because of severe heart failure and sustained ventricular tachycardia. She had been diagnosed as having ocular sarcoidosis and also received permanent pacing due to complete atrioventricular block for 10 years. Her echocardiogram showed wall thinning of the basal interventricular septum (open arrow heads) and left ventricular apex (closed arrow head) (a), and severe functional mitral regurgitation even after CRT-D (b).
2. New attempts for early diagnosis of cardiac sarcoidosis

While the incidence of cardiac involvement ranges widely from 27 to 76% of patients with systemic sarcoidosis, studies have agreed that the rate of ante-mortem diagnosis is ≤ 50% [4, 5]. Another report found that the conventional echocardiographic findings attributed to cardiac lesions could be seen in only 14% of patients with systemic sarcoidosis [6]. Taking into account the incidence of cardiac involvement, 2-dimensional echocardiography is not sensitive to diagnose cardiac sarcoidosis. Therefore, various attempts have been made to achieve early detection.

2-1. Ultrasonic tissue characterization

It has been reported to apply ultrasonic tissue characterization with integrated backscatter (IBS), which measures acoustic properties, for the diagnosis of early myocardial involvement [18]. They recognized a decreased cycle dependent variation of IBS in the basal IVS in 8 patients in whom 2-dimensional echocardiography did not reveal any abnormal findings, but radionuclide testing, including FDG-PET, enabled early detection of cardiac sarcoidosis. The segmental wall motion abnormalities were not seen; therefore, changes in IBS might reflect early lesions such as myocardial fibrosis and cellular infiltration.

2-2. Transesophageal echocardiography

Hourigan and colleagues reported an atrial involvement causing transient atrial wall hypertrophy by transesophageal echocardiography [19]. Sarcoid involvement was only seen in the atrium in this case. As mentioned above, about 20% of patients with cardiac sarcoidosis have atrial lesions, and the atrial involvement is less common than that of the ventricle [2]. Needless to say, echocardiography can not differentiate atrial wall hypertrophy caused by sarcoid involvement from those by the other origins, such as tumor invasion or lipomatous hypertrophy [20, 21]. However, in a small number of patients with atrial involvement, transesophageal echocardiography could also contribute to early diagnosis by combining other clinical information and images.

2-3. Possible future contribution

Novel technology has enabled echocardiographic measurement of myocardial strain. The widespread clinical availability of strain has been expected to resolve the ongoing difficulties in quantification of regional performance despite many technical limitations [22]. As described before, the patients with cardiac sarcoidosis often reveal scattered distribution of wall motion abnormalities independent of territory of major epicardial coronary arteries. The assessment of wall motion is occasionally complicated because LV wall movement is influenced by the adjacent myocardium (tethering) and the motion of the whole heart (translation). The measurement of strain certainly could be useful in the assessment of these wall motion abnormalities by providing information on regional performance independent of both tethering and translation. Additionally, recent developments with magnetic resonance imaging (MRI) demonstrate a unique feature of myocardial sarcoidosis. Most subjects show late enhancement in the myocardium transmurally; however, it can be seen only in the subepicardium, not in the subendocardium in some subjects [23]. This suggests that only the subepicardium is involved with myocardial sarcoidosis in some patients. This is quite different from those with coronary artery disease, in which late enhancement should necessarily accompany subendocardium involvement because of ‘wave-front’ disease progression from the endocardium to epicardium. These findings were consistent with a past pathologic study [5]. It has been recently demonstrated that the transmural myocardial strain profile enables assessment of subepicardial myocardial viability in the canine model of subendocardial infarction [24]. In the future, this method could facilitate diagnosis of cardiac sarcoidosis by detecting subepicardial myocardial injury.

3. Predicting LV remodeling and function after corticosteroid therapy using echocardiography

The long-term benefit of corticosteroid therapy for cardiac sarcoidosis has not been established [3, 8]. However, since the natural prognosis of cardiac sarcoidosis remains poor, steroid therapy is commonly performed for symptomatic patients with either definite diagnosis or strong probabilities [3]. There remains controversy about the optimal initial dose and duration of steroid therapy. However, treatment with a low initial dose (≤ 30 mg daily) of prednisone has been proven equally sufficient as the high initial dose (≥30 mg daily) hitherto prescribed [25]. The use of 30 mg of prednisone daily for 4 weeks, with a gradual tapering to a maintenance dose of 5-10 mg daily is currently the most widespread protocol in Japan [26]. A careful
evaluation using echocardiography needs to be performed to confirm the effect of treatment [27].

In order to clarify the effects of steroid therapy on cardiac function, we retrospectively investigated the prognosis of cardiac sarcoidosis and the changes in cardiac function as assessed by echocardiography in 43 patients who received long-term steroid therapy (mean follow-up period of 88 months) [28]. The patients were divided into 3 groups based on EF prior to steroid therapy (Group A: EF ≥55%, Group B: 30 ≤EF <55%, and Group C: EF <30%). In Groups A and C, LV end-diastolic volume index (EDVI) and EF did not change before and after steroid administration. In Group B, both EDVI and EF improved significantly after steroid administration (Figure 10). None of the patients died during a 10-year follow-up period in Group A. However, survival in Group C was clearly lower with a 10-year survival of 19% (Figure 11). This suggests that steroid therapy obviously improves cardiac function in selected patients with cardiac sarcoidosis. LV function did not deteriorate in Group A, which might suggest steroid therapy has the protective effects of preventing LV remodeling and deterioration of LV function in the early stage of the disease. Despite the retrospective and relatively small-scale study similar to ours, the other study also demonstrated that New York Heart Association (NYHA) functional class at the initiation of steroid therapy was one of the most significant predictors of mortality [25]. Therefore, when cardiac sarcoidosis is definitively diagnosed, steroid therapy should be started even when cardiac function is still normal and a patient is asymptomatic. However, steroid therapy could be ineffective in patients with severe LV dysfunction. In such cases, invasive therapeutic procedures such as implantable cardioverter defibrillation (ICD) and cardiac resynchronization therapy (CRT) should be positively performed to improve prognosis [29].

References


Fig.10. Comparison of the left ventricular end-diastolic volume index (EDVI) and ejection fraction (EF) among 3 groups of 43 patients with cardiac sarcoidosis according to EF prior to steroid therapy. Black and white columns correspond to before and after steroid therapy, respectively. Reproduced from Chiu C-Z, Nakatani S, Zhang G, et al. Prevention of left ventricular remodeling by long-term corticosteroid therapy in patients with cardiac sarcoidosis. Am J Cardiol 2005; 95: 143-6.


102: 1400-6.