Deterioration of Cardiac Function during the Progression of Cardiac Sarcoidosis: Diagnosis and Treatment

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Abstract

The cardiac involvement of sarcoidosis causes progressive heart failure symptoms and is a life-threatening condition; thus, an early and appropriate diagnosis of this condition is crucial. On the other hand, the decline in the cardiac function is rapid; therefore, patients usually have moderate-severe left ventricular dysfunction when diagnosed with cardiac sarcoidosis, which may decrease the effectiveness of therapies. We herein report three illustrative cases of heart failure due to cardiac sarcoidosis in patients who were or were not diagnosed with preceding systemic sarcoidosis. We also discuss the currently available diagnostic modalities and possible biomarkers for the diagnosis of cardiac sarcoidosis.

Key words: cardiac sarcoidosis, cardiac function, congestive heart failure

Introduction

The clinical presentation of sarcoidosis with cardiac involvement may depend on the extent and location of the granulomatous processes (1, 2). The most frequent cardiac manifestations of cardiac sarcoidosis (CS) include conduction disturbances and arrhythmias, sudden death and congestive heart failure (CHF), the latter being reported in up to 30% of affected patients (3-9). Increased awareness, early medical treatment, the use of pacemakers and implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy with ICD (CRTD) are changing the causes of death in CS patients, with CHF becoming the most common cause.

Yazaki et al. followed 95 CS patients for a mean period of 68 months. Of these, 40 died, and 73% of the deaths were associated with heart failure. The hearts of patients with sarcoidosis-associated CHF often display a similar morphology to that of patients with idiopathic dilated cardiomyopathy (DCM). In a study of more than 100 patients undergoing left ventriculoplasty for idiopathic DCM, we found that 7% actually had CS, which had been undiagnosed prior to the cardiac symptoms (9). Yazaki et al. demonstrated a five-year survival rate of 37% in patients with sarcoidosis and 64% in patients with idiopathic DCM; both groups had a similar New York Heart Association (NYHA) functional class and left ventricular ejection fraction (LVEF) (10). Therefore, the prognosis of CS may be worse than that of idiopathic cardiomyopathy, and the onset and severity of CHF may be a prognostic indicator of CS. On the other hand, the prognosis of the patients with CS and DCM has recently been improving due to the use of evidence-based therapies and/or early detection of the disease. In a systematic review of the mortality data in patients with CS, it was found that the five-year survival now ranges from 75% to 100%, and that the extent of left ventricular (LV) dysfunction is the strongest predictor of survival (11).

Considering that CS, when untreated, causes progressive heart failure, which is frequently life-threatening, early detection of the cardiac sarcoid involvement and the initiation of appropriate therapies is mandatory; however, patients diagnosed with CS usually have advanced LV dysfunction at the time of diagnosis of the CS (12). This is in part due to the fact that cardiac dysfunction may occur suddenly and progresses rapidly in the patients with systemic sarcoidosis, who may not be followed-up very frequently as outpatients.

In the present study, we report three illustrative cases of CHF and review the clinical issues associated with CS, with special reference to the deterioration of the cardiac function.
Case 1

A 51-year-old woman was admitted to our hospital with sudden-onset symptoms of heart failure, which had started about one month earlier. She reported no history of systemic sarcoidosis. Echocardiography showed LV enlargement and a diffusely decreased LVEF. She had undergone echocardiography 2.4 years prior, which showed a normal ejection fraction (Fig. 1). Chest X-rays demonstrated cardiomegaly and right hilar lymph node enlargement (Fig. 2A). An electrocardiogram (ECG) showed normal sinus rhythm, albeit with prolonged PQ intervals, incomplete right bundle branch blocks, low voltages in the limb leads and ST-T abnormalities (Fig. 2B). These changes in X-rays and ECG indicators were not observed in the ECG obtained 2.4 years earlier, except for slight PQ prolongation (Fig. 2C).

On admission, the patient’s plasma brain natriuretic peptide (BNP) levels were markedly elevated (706 pg/mL). Coronary angiography showed normal coronary arteries, and left ventriculography showed hypokinesis of the anterior and inferior walls (Fig. 2D, E). A histological examination of biopsied endomyocardial samples revealed the infiltration of mononuclear cells and enhanced fibrosis, although sarcoidosis-like granulomatous formations were not detected (Fig. 2F). The serum angiotensin-converting enzyme (ACE) activity (17.0 IU/L) and soluble interleukin-2 receptor (sIL-2 R; 395 U/mL) levels were within the normal limits. Therefore, we tested her for possible CS in further imaging examinations.

During progressive congestive cardiomyopathy. We also discuss the rate of the decrease in cardiac contractility in patients diagnosed or undiagnosed with systemic sarcoidosis without known cardiac abnormalities prior to the emergence of the cardiac manifestations.

Figure 1. The temporal changes in the LV end-diastolic dimension (LVDd; vertical axis in A, mm) and LVEF (vertical axis in B, %) on the echocardiograms of the three patients. The horizontal axis represents years, and the 0 indicates the time at which cardiac sarcoid involvement was diagnosed. The pink dotted lines represent 55 mm LVDd in A and 50% LVEF in B, which are critical levels considered to indicate the progressive deterioration of the LV function in cardiac sarcoidosis.

Cardiac magnetic resonance (CMR) imaging demonstrated late gadolinium (Gd) enhancement (LGE) from the mid-wall to the epicardial sites of the anteroseptal, anterolateral and inferior walls of the left ventricle (Fig. 3A, D). T2-weighted CMR showed high-intensity signal areas between the endomyocardial and mid-ventricular regions (Fig. 3B, E), whereas 99m-technetium myocardial scintigraphy showed perfusion defects on the basal areas and on the anterolateral wall of the left ventricle (Fig. 3C, F). Subsequent 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) showed increased nuclear uptake in the myocardium and the hilar, para-aortic and subclavian lymph nodes (Fig. 4A-C).

The cytology of fine-needle aspiration samples obtained from the right supraclavicular lymph node clearly showed multinucleated giant cells (Fig. 4D). To confirm the absence of tuberculosis, nodal biopsies were examined, which revealed noncaseating-epithelioid cell granulomas with multinucleated giant cells, confirming the diagnosis of sarcoidosis (Fig. 4E) (13). Following the diagnosis of systemic sarcoidosis with cardiac involvement, prednisolone treatment was initiated at a dose of 60 mg/day every other day; this dose was gradually tapered to 20 mg/day every other day and has been maintained.

Case 2

A 57-year-old woman with lung and lymph node sarcoidosis that had been histologically diagnosed from biopsy specimens two years earlier was transported by ambulance to an emergency center after developing cardiogenic shock. Chest X-rays demonstrated cardiomegaly and pulmonary congestion. ECG analyses showed ventricular tachycardia (VT; Fig. 5A), which was cured to sinus rhythm using electrical cardioversion. Coronary angiography showed no significant luminal stenosis, but left ventriculography showed severe diffuse hypokinesis, particularly in the basal regions (areas 1 and 5). The patient was transferred to our hospital...
The previous F-FDG PET analyses had demonstrated enhanced nuclear uptake in the lung and hilar and mediastinal lymph nodes, but not in the heart. Cardiac biopsies were not obtained, because informed consent was not obtained. An ICD was implanted and corticosteroid therapy was initiated at a dose of 60 mg/day every other day; this dose was gradually tapered to 5 mg/day every day and has been maintained.

Case 3

In a previous study, we analyzed the clinical history of 54 patients diagnosed with systemic sarcoidosis (14). Among these patients, two were not diagnosed with CS and were eventually diagnosed with cardiac involvement during the follow-up. One of these patients was a 69-year-old man with systemic, but not cardiac, sarcoidosis confirmed by lymph node biopsy. The patient had previously undergone periodic follow-up with electrocardiography and echocardiography for possible cardiac involvement. Although his LVEF was within the normal range at the time of follow-up, it suddenly declined (Fig. 1). The \(^{18}\)F-FDG PET study showed increased nuclear uptake in the lung and hilar and mediastinal lymph nodes, but not in the heart. Cardiac biopsies were not obtained, because informed consent was not obtained. An ICD was implanted and corticosteroid therapy was initiated at a dose of 60 mg/day every other day; this dose was gradually tapered to 5 mg/day every day and has been maintained.

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Figure 2. The chest X-ray, electrocardiogram (ECG), left ventriculography and cardiac biopsy findings for case 1. The chest X-ray showed cardiomegaly (cardiothoracic ratio of 60%) and enlargement of the right hilar lymph nodes (A). The ECG showed normal sinus rhythms, PQ prolongation, incomplete right bundle branch block, low voltage in the limb leads and ST-T abnormalities (B). An ECG obtained 2.4 years earlier showed only slight PQ prolongation (C). Left ventriculography showed diffuse hypokinesis, particularly in the anterior (areas 1-2, arrows) and inferior walls (areas 3-4, arrow heads; D, end-diastolic phase; E, end-systolic phase). The histological evaluation of the endomyocardial biopsies showed the infiltration of mononuclear cells and enhanced fibrosis (F, scale bar indicates 50 μm).
showed fibrotic degeneration with the infiltration of CD45-positive lymphocytes and CD68-positive monocytes/macrophages, although granulomatous changes were not detected (Fig. 7C). Sustained VT was documented, and after the diagnosis of cardiac sarcoid involvement, corticosteroid therapy was initiated and a CRTD was implanted.

As indicated in Fig. 1, the CHF progressed rapidly within only a few months or years in all three cases, sometimes in association with ventricular tachyarrhythmias. The data from the present cases suggest that a LV end-diastolic dimension <55 mm and a LVEF <50% may be critical factors indicating the progressive deterioration of the LV function in CS patients.

**Strategies for Diagnosing Cardiac Sarcoidosis**

**CMR imaging**

In cases with cardiac involvement of sarcoidosis, the myocardium is replaced by fibrotic fibrogranulomatous tissue. These fibrotic changes in the heart can be observed using magnetic resonance imaging (MRI) with the LGE technique. Previous studies demonstrated that characteristic LGE patterns and locations are diagnostic of CS, and that CMR imaging with LGE facilitates the prediction of the LV function. T2-weighted MRI has also been used to detect acute inflammatory processes associated with myocardial sarcoidosis in CS patients (15). Therefore, T2-weighted sequences may provide increased sensitivity for predicting progressive deterioration in the cardiac function in CS patients.

In case 1 in the present study, CMR imaging demonstrated LGE that may represent chronic myocardial damage (16) from the mid-wall to the epicardial sites. In addition, T2-weighted CMR, which can demonstrate acute inflammation or edema (16), showed high-intensity signal areas between the endomyocardial and mid-ventricular regions. These findings collectively suggested that the inflammation-associated injury had migrated from the epicardial region to the endomyocardial region.

Matoh et al. studied 12 sarcoidosis patients using Gd-MRI, myocardial perfusion single photon-emission computed tomography (SPECT) (17), gallium-67 citrate (Ga-67) scintigraphy and/or 18F-FDG PET. LGE was observed in five patients, and was positive in 39 (39%) of 100 LV segments. LGE was distributed primarily from the mid- to the epicardium, and the lack of perfusion defects on myocardial perfusion SPECT was more prominent in less transmural LGE segments. Two patients with diffuse LGE and one case with focal LGE exhibited positive cardiac uptake on Ga-67 scintigraphy, while two other patients with focal LGE showed cardiac uptake on 18F-FDG PET. The authors concluded that LGE was useful for diagnosing CS and evaluating the cardiac function, suggesting that the distribution of LGE from the mid- to the epi-myocardium is characteristic.
of CS, and that larger LGE areas correlate with poor LV function.

Ichinose et al. analyzed the topographic localization of myocardial lesions on CMR imaging and their relationships...
with the plasma BNP levels and cardiac function parameters in 10 CS patients. Myocardial hyperenhancement was significantly more common in the subepicardial layers than in the subendocardial layers (18). Moreover, the authors showed a significant correlation between the global extent of LGE and the plasma BNP levels, and a negative correlation between the LV end-diastolic volume indices and LVEF in CS patients. Therefore, the extent of myocardial lesions may be related to the LV dysfunction and plasma BNP levels in CS patients.

Watanabe et al. retrospectively evaluated 17 CS patients who were diagnosed according to the 2006 revised guidelines of the Japanese Ministry of Health and Welfare (13) and underwent CMR imaging (19). In that study, the LGEs were located, and the relationship between the LGE and LVEF characteristics and duration of sarcoidosis was evaluated. While the LGE was most frequently found in the subepicardial layer, the affected LGE segments were correlated with the LVEF (r=-0.84, p<0.0001) and LV diastolic volumes (r=0.88, p<0.0001). Transmural lesions were also significantly more common in patients with an LVEF of 35% or lower than in those with an LVEF greater than 35% (p=0.0004). All patients with an LVEF of 35% or lower had both subepicardial and transmural lesions, and the affected LGE segments were positively correlated with the duration of sarcoidosis originating in the extracardiac organs (r=0.76, p=0.005). The authors concluded that CMR imaging with LGE facilitates the diagnosis of CS and predicts the LV function.

Patel et al. performed an observational study of 152 patients with biopsy-identified extra-cardiac sarcoidosis (20), no known cardiac sarcoidosis, and an LVEF of ≥50%. The presence of LGE in the LV myocardium was considered to be diagnostic for CS. Compared with patients without LGE, those with LGE had higher heart rates (84±19 vs. 76±18 bpm, p=0.002), a greater prevalence of abnormal ECGs (76 vs. 31%, p<0.001), more diastolic dysfunction (67 vs. 33%, p=0.05), a decreased right ventricular ejection fraction (49±8

**Figure 6.** The CMR and myocardial scintigraphy findings for case 2. Long- (A) and short- (B) axis CMR images showed LGE at the epicardial site of the mid-basal portions of the left ventricle (arrows), but not the lateral wall. The short axis showed black-blood T2-weighted images demonstrating hyperintense signals at the endocardial and mid-wall sites of the anterolateral-inferoseptal wall (C, arrows). 99m-technetium myocardial scintigraphy showed perfusion defects in the basal part of the anteroseptal-inferoposterior wall of the left ventricle (D).

**Figure 7.** The 18F-FDG PET, CMR and cardiac biopsy findings for case 3. 18F-FDG PET showed abnormal uptake in the heart (arrows) and cervical, mediastinal and hilar lymph nodes (A). CMR showed LGE at the epicardial site of the anteroseptal-lateral wall of the left ventricle (B, arrows). The histological study of an endomyocardial biopsy sample showed fibrotic degeneration with the infiltration of mononuclear cells (C, scale bar indicates 50 μm). Most mononuclear cells were CD45-positive lymphocytes or CD68-positive monocytes/macrophages (data not shown), although granulomatous changes were not detected.
vs. 55±6%, $p=0.012$), and evidence of non-sustained VT (33 vs. 6%). The authors concluded that patients with sarcoidosis and preserved systolic function commonly had myocardial damage, which may increase the risk of ventricular tachyarrhythmias.

**18F-FDG PET**

More recently, \(^{18}\)F-FDG PET has been increasingly used for the evaluation and monitoring of CS patients (21-23). Accordingly, \(^{18}\)F-FDG PET imaging plays a significant role in the clinical diagnosis, assessment of disease activity, monitoring of therapeutic responses and evaluation of the prognoses of CS patients (24). In \(^{18}\)F-FDG PET imaging for CS, the patterns of glucose metabolism and myocardial perfusion are known markers of inflammation. Whereas enhanced glucose metabolism with normal perfusion indicates active inflammation, decreased perfusion with high glucose metabolism represents advanced stage disease, and absent or decreased perfusion with limited glucose metabolism indicates end-stage CS. It should be noted that, for appropriate interpretation of the PET images, the suppression of physiological myocardial \(^{18}\)F-FDG PET uptake is crucial, which can be achieved by fasting, dietary carbohydrate restriction and the administration of heparin before the nuclear injection (25).

McArdle et al. (26) compared the locations and degrees of FDG uptake in 20 CS patients with either advanced atrioventricular block (AVB) or VT and compared the results with those of seven CS patients without AVB or VT. Both the mean LV standardized uptake (SUV) values and maximum SUV in the CS patients with VT were significantly higher than those in CS patients with AVB (mean SUV: median VT, 5.33; range 4.7-9.35 vs. median AVB, 2.48; range 0.86-8.59; $p=0.016$; Max SUV: median VT, 11.07; range, 9.24-14.4 vs. median AVB, 5.63; range 3.42-15.71, $p=0.005$) and those in control patients. The SUV values did not differ significantly between the AVB patients and controls. The receiver-operator characteristic (ROC) analyses were used to identify patients with VT, and showed areas under the curve (AUCs) of 0.93 and 0.895 for a mean LV SUV value of $>3.42$ and a maximum SUV value of $>8.56$, respectively ($p<0.001$). Moreover, the mean overall LV SUV value was correlated with the number of abnormal segments determined by a visual analysis (Spearman’s coefficient $=0.506$, $p=0.006$) and was negatively correlated with the resting LVEF (Spearman’s coefficient $=-0.42$, $p=0.024$). In addition, the mean EF was measured using gated rest PET perfusion scanning and was found to be lower in VT patients than in AVB patients (median VT, 33%; range 15-56 vs. median AVB, 51%; range 18-71, $p=0.082$) and significantly lower in VT patients than in clinically silent CS patients ($p=0.0026$). These observations suggest that there is a relationship between the degree of abnormal FDG uptake and the clinical presentation, particularly with reference to ventricular tachyarrhythmia and decreased LV function. Further prospective studies are required to confirm these relationships.

Mehta et al. (27) evaluated 62 ambulatory patients with sarcoidosis and diagnosed CS by assessing abnormalities detected using CMR imaging or \(^{18}\)F-FDG PET. CS patients were referred for risk stratification by electrophysiology (EPS). Among the 62 patients examined, the prevalence of CS was 39%, and CS patients were more likely to have abnormal Holter ECG recordings (50 vs. 3%, $p=0.001$) and echocardiographic parameters (25 vs. 5%, $p=0.02$). The degree of pulmonary impairment was not predictive of CS. Two of the 17 patients analyzed using EPS had abnormal test findings and received ICDs. Over a mean follow-up of 1.8 years, no patient died or exhibited ventricular arrhythmias, and the authors concluded that the sarcoid lesions identified on \(^{18}\)F-FDG PET are not predictive of arrhythmias in patients with preserved cardiac function.

Matthews et al. (28) described a patient with CHF and biopsy-diagnosed sarcoidosis whose imaging data were consistent with cardiac involvement, as evidenced by extensive \(^{18}\)F-FDG uptake into the ventricles and multiple focal areas of myocardial hyperintense signals on T2-weighted CMR images and corresponding areas of LGE. Significant clinical improvements were observed after the initiation of medical therapy for CHF and corticosteroids. Subsequent follow-up CMR imaging studies performed three and nine months later demonstrated improvements in the LVEF and the almost complete disappearance of abnormal T2 signals, with persistent LGE. However, the three- and 12-month \(^{18}\)F-FDG PET analyses demonstrated complete resolution of all cardiac and extracardiac sarcoid activity. Therefore, although both the CMR and \(^{18}\)F-FDG PET analyses facilitated the diagnosis of CS, only \(^{18}\)F-FDG PET imaging demonstrated serial assessments that reflected the disease activity in response to therapy.

**Hybrid PET/MRI**

Rischpler et al. reviewed a comparative summary of the existing applications for hybrid PET/MRI in the field of cardiology, and suggested potential cardiac applications that exploit the unique properties of the newly introduced combined instrumentation (29). Integrated hybrid PET/MRI analyses allow for the assessment of the quantity of affected myocardium using LGE, facilitate the assessment of disease stage and help in treatment decision-making. Moreover, this technique may be used to assess CS-related inflammatory cardiomyopathy.

White et al. reported a patient in whom simultaneous PET/MRI was used to diagnose active CS (30). Interestingly, intrinsic spatial regions of increased \(^{18}\)F-FDG uptake were found in the subepicardial LGE zone, indicating possible fibrosis and suggesting inward migration of the inflammatory injury. Subsequently, \(^{18}\)F-FDG PET and cardiac MRI were exploited as a hybrid technique for diagnosing active CS. Therefore, using cardiac PET/MRI may be clinically feasible and effective for the detection of inflammatory cardiac disease.
**Echocardiography**

Kaderli et al. evaluated the LV function using conventional echocardiography and tissue Doppler imaging in 55 patients with early stage pulmonary sarcoidosis without cardiac involvement, and compared the findings with those of 22 healthy subjects. The isovolumetric acceleration (IVA) is a measure of LV contractility that is determined by non-invasive tissue Doppler imaging (31). The IVA was lower in patients with sarcoidosis than in healthy controls, and the ratio of the myocardial pre-contraction time (PCTm) and contraction time (CTm) was higher at the septal annulus (p=0.026). The IVA values in both the lateral and septal annuli were also significantly lower in the sarcoidosis group than in the control group. These observations may reflect subclinical myocardial sarcoid involvement, particularly that of the interventricular septum. The authors concluded that these analyses may contribute to clinical decision-making by facilitating the predictions of cardiac involvement in patients with pulmonary sarcoidosis.

Focardi et al. evaluated 69 patients with chronic sarcoidosis without suspected cardiac involvement and 26 control subjects using echocardiography, and determined the prevalence of LV systolic and diastolic dysfunction in patients with chronic sarcoidosis without clinical evidence of heart disease (32). No significant differences were observed in the atrial size, LV diameter, wall thickness, LVEF or endocardial fractional shortening (FS) between the sarcoid and control patients. However, the sarcoid patients had lower mid-wall fractional shortening (mFS). Taken together, these observations demonstrated the absence of LV systolic dysfunction, as evaluated by traditional echocardiographic methods, in patients with chronic sarcoidosis, and an absence of any relationship between LV diastolic dysfunction and sarcoidosis. Only the mFS was lower among sarcoid patients, particularly in those with a long disease history. Further analyses are required to confirm the significance of this index as a potential marker of cardiac involvement in patients with chronic sarcoidosis.

**Cytokines**

Extensive myocardial sarcoid granulomatous infiltration results in DCM and heart failure, which can be either systolic or diastolic in nature. However, studies of autopsy hearts have demonstrated that granulomatous infiltration is not distributed diffusely, but instead appears in patches. Therefore, it is speculated that, in addition to direct injury from granulomas with myocardial cell loss and interstitial fibrosis, other factors, such as proinflammatory cytokines, may play a role in myocardial dysfunction, particularly in the acute or subacute phase of CHF in CS patients.

The levels of inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6) and their soluble receptors, are reportedly increased in CHF patients (33, 34). Inflammatory cytokines may modulate the myocardial functions through a variety of mechanisms, including stimulation of hypertrophy and fibrosis through direct effects on cardiomyocytes and fibroblasts, the impairment of myocardial contractile function through direct effects on intracellular calcium transport and adrenergic receptor signaling, the induction of apoptosis and increasing the expression of genes involved in myocardial remodeling (35).

**Type 1 helper T cell (Th1)-related cytokines**

The expression of Th1-related cytokines is enhanced by sarcoidosis. Therefore, we investigated the inflammatory cytokine mRNA expression in the myocardia of 12 CS and 10 idiopathic DCM patients (36). These analyses showed significantly enhanced expression of Th1-related cytokines, such as IL-12p40, IFN-γ and IL-2, in CS patients, and myocardial immunostaining demonstrated that the enhanced expression of IL-12 was confined to macrophages and giant granuloma cells. These data suggest that the expression patterns of the Th1-related cytokines IL-12 and IFN-γ may be differentially diagnostic of cardiac dysfunction in patients with idiopathic DCM and CS.

**TNF-α**

TNF-α is known to be a major proinflammatory cytokine that controls the strength, effectiveness and duration of local and systemic inflammatory reactions. Numerous studies have confirmed high TNF-α production in cases with sarcoidosis, and have shown an important role of TNF-α in granuloma formation (37-41). Moreover, mononuclear phagocytes, such as mature macrophages, are responsible for the TNF-α secretion in patients with sarcoidosis (42). In the study of the inflammatory cytokines described above, TNF-α mRNA was expressed in the myocardia of both CS and idiopathic DCM patients, but it tended to be higher in the sarcoid myocardia.

Takashige et al. (43) investigated TNFA (TNF-α) and TNFB (lymphotoxin-alpha) gene polymorphisms in 26 CS patients of Japanese origin. Significant increases in the TNFα2 allele were found in the patient group, suggesting that the TNFA gene is involved in the genetic susceptibility to CS. Subsequently, HLA-DQB1*0601 was found to be the allele most significantly associated with CS susceptibility, and was more significantly increased compared with TNFα2 (44). Kuroda et al. also analyzed single nucleotide polymorphisms and showed that the TNF-α-857C/T polymorphism may affect the susceptibility to CS (45).

The chimeric monoclonal anti-TNF-α antibody, infliximab, has been approved for use in patients with rheumatoid arthritis and Crohn’s disease. Case reports (46-50) have described the success of infliximab in patients with sarcoidosis refractory to conventional therapy. Although the benefits and indications have not been established in patients with sarcoidosis, these reports suggest that anti-TNF-α therapy may be effective in patients with certain phenotypes.

Crouser et al. reported five consecutive patients with CD4+ lymphopenia and assessed the clinical disease mani-
Table 1. Clinical Characteristics of Patients with CD4+ Lymphopenic Sarcoïdosis*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Race</th>
<th>Disease manifestations</th>
<th>Clinical improvement post infliximab</th>
</tr>
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<tbody>
<tr>
<td>S1</td>
<td>60</td>
<td>M</td>
<td>W</td>
<td>Lung, LN, hrt, sinus</td>
<td>Lung a, hrt b, sinus c</td>
</tr>
<tr>
<td>S2</td>
<td>41</td>
<td>M</td>
<td>AA</td>
<td>Lung, LN, hrt, sinus</td>
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</tr>
<tr>
<td>S3</td>
<td>65</td>
<td>F</td>
<td>W</td>
<td>Lung, LN, sinus</td>
<td>Sinus c</td>
</tr>
<tr>
<td>S4</td>
<td>57</td>
<td>M</td>
<td>W</td>
<td>Lung, LN, skin</td>
<td>Skin d</td>
</tr>
<tr>
<td>S5</td>
<td>58</td>
<td>M</td>
<td>AA</td>
<td>Lung, LN, hrt, eyes</td>
<td>Lung a, hrt b, eyes c</td>
</tr>
</tbody>
</table>


a A > 10% increase in FVC, total lung capacity, or diffusing capacity was observed.
b Initial left ventricular ejection fraction was < 45% with ≥ 10% subsequent increase.
c Resolution of chronic sinus symptoms (recurrent infections, congestion) was reported.
d Objective improvement in sarcoidosis-mediated skin rash was observed.
e Resolution of uveitis was documented.


festations and peripheral blood T-cell subsets before and after infliximab treatment (51). Significant increases in the absolute peripheral blood lymphocyte and CD4+ T-cell counts were observed, and improvements in the clinical disease manifestations were demonstrated in all infliximab-treated patients. The authors concluded that the presence of CD4+ lymphopenia identified a distinct sarcoidosis phenotype that is particularly responsive to anti-TNF-α therapy. Interestingly, in three of five patients, the initial LVEF values were less than 45% and were subsequently increased by more than 10% after anti-TNF-α therapy (Table 1).

Other biomarkers

Several biological markers, including ACE, lysozyme and sIL-2R, have been recognized during assessments of sarcoidosis activity (52) (Table 2). However, the sensitivity and specificity of those biomarkers are often inadequate for CS, which requires better biomarkers. Although several new biomarkers of CS have been reported, none are genuinely specific to CS. Therefore, integrative diagnoses require imaging and histological examinations, although the future diagnosis rates may be improved by the use of multiple biomarkers.

Atrial natriuretic peptide (ANP) and BNP

In a study of 62 patients, Yasutake et al. showed a tendency for there to be increased plasma ANP and BNP levels in 27 CS patients, and demonstrated the utility of the ROC analyses of these markers for distinguishing among high-degree AVB, VT and CHF (53).

Myeloid-related protein complex (MRP 8/14)(S100A8/9)

MRP 8/14 is a member of the S100 family of inflammation-related proteins and is expressed in activated macrophages and granulocytes. We compared the serum levels of MRP 8/14 in 30 normal subjects, 23 patients with idiopathic DCM, 25 sarcoïd patients without CS and 10 patients with CS (54). The serum MRP 8/14 levels were only significantly elevated in the CS patients, who had enhanced immunohistochemical expression in macrophages and giant cells of granulomas from myocardial tissues. Therefore, the assessment of MRP 8/14 expression may facilitate the diagnosis of CS.

High-sensitive cardiac troponin T (hs-cTnT)

Baba et al. evaluated the sensitivity and specificity of hs-cTnT, BNP, ACE, lysozyme, CMR and Ga-67 scintigraphy using 18F-FDG PET data as an indicator of sarcoidosis activity in 12 CS patients (55). The data showed that the sensitivity and specificity of hs-cTnT were 87.5% and 75%, respectively, and the positive and negative predictive values were 87.5% and 75%, respectively. These investigators concluded that hs-cTnT was an excellent marker for evaluating the disease activity in CS patients, with superior sensitivity

Table 2. Possible Biologic Markers of Sarcoïdosis Activity*

<table>
<thead>
<tr>
<th>Monocyte Origin</th>
<th>Neutrophil associated</th>
<th>Extracellular matrix associated</th>
<th>Lymphocyte associated</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin converting enzyme</td>
<td>Collagenase</td>
<td>Procollagen III peptide</td>
<td>Soluble interleukin-2 receptors</td>
<td>Beta 2-microglobulin</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Elastase</td>
<td>Hyaluronan</td>
<td>CRP</td>
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<td>Calcitriol</td>
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<td>Fibronectin</td>
<td>ESR</td>
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<td>Kininase</td>
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<td>Amyloid</td>
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and negative predictive values and a good responsiveness to steroid therapy.

**High-sensitive cardiac troponin I (hs-cTnI)**

Tanada et al. reported the case of a CS patient and determined the serum hs-cTnI levels over time. Both the serum hs-cTnI and N-terminal proBNP (NT-proBNP) levels were increased before the initiation of steroid therapy and decreased following treatment (56). While the level of NT-proBNP was transiently elevated, possibly because of body fluid retention associated with steroid therapy, the hs-cTnI levels did not increase; they decreased with the proceeding therapy. These data indicate that hs-cTnI may indicate myocardial cytopathy in CS patients, and may have potential as a biomarker of therapeutic responses.

**Conclusion**

The understanding of CS etiology and disease states has advanced considerably in recent years, and the diagnostic and treatment approaches have improved accordingly (57). However, the temporal changes in cardiac function among patients with sarcoidosis remain poorly characterized. CHF usually progresses rapidly within a few weeks or months in CS patients, and this is sometimes associated with conduction or rhythmic abnormalities that reflect gross myocardial granulomatous infiltration. In addition, the influence of inflammatory cytokines, such as TNF-α, may be an important factor in the pathogenesis of progressive congestive cardiomyopathy in patients with CS. Biomarkers, including high-sensitive cardiac troponins, may also be predictive of LV dysfunction.

The observation of both an abnormal uptake on 18F-FDG PET and abnormal CMR imaging (LGE, and particularly hyperintensity on T2-weighted images) may therefore make it clinically possible to detect active inflammation and to thus predict a deteriorating LV function in CS patients. However, because histopathological confirmation of myocardial sarcoid lesions cannot be obtained in individual patients, it remains unclear whether subacute or chronic myocardial sarcoid lesions are accurately reflected by these imaging modalities, which may also influence the LV function.

Finally, the establishment of optimal diagnostic and therapeutic strategies for CS patients and the preservation of their LV function remains a challenge, and these topics warrant thorough prospective multicenter trials.

**The authors state that they have no Conflict of Interest (COI).**

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