

[ CASE REPORT ]

## Clinical Features and Histopathology of Cardiac Sarcoidosis with Refractory Heart Failure: An Autopsy Case

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### Abstract:

Treatment involving the insertion of an implantable cardioverter defibrillator and cardiac resynchronization therapy devices has markedly improved the prognosis of cardiac sarcoidosis. However, the prognosis remains poor in patients with advanced cardiac dysfunction or heart failure. We herein report the clinical course and histopathological findings of the autopsied heart of a patient with cardiac sarcoidosis with long-term refractory heart failure.

**Key words:** sarcoidosis, prognosis, heart failure, pathology, dilated cardiomyopathy

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### Introduction

In recent years, advancements in diagnostic imaging modalities, such as cardiac magnetic resonance and <sup>18</sup>F-fluorodeoxyglucose positron emission tomography (FDG-PET), as well as the accumulation of cases have allowed for a more accurate diagnosis of cardiac sarcoidosis (1). Treatment involving the insertion of implantable cardioverter defibrillator and cardiac resynchronization therapy devices has markedly improved the prognosis for cardiac sarcoidosis. However, the prognosis remains poor in patients with advanced cardiac dysfunction or heart failure. Unfortunately, little information has been available regarding the details of patient with a long-term severely deteriorated cardiac function.

We herein report the clinical course and histopathological findings of the autopsied heart of a patient with cardiac sarcoidosis with long-term refractory heart failure.

### Case Report

A 53-year-old man developed atrioventricular block in 1998, at 34 years of age, and a permanent pacemaker was

implanted at a nearby hospital (HMC). At that time, bilateral hilar lymphadenopathy (BHL) was observed, and a trans-bronchial lung biopsy (TBLB) revealed non-caseating epithelioid cell granulomas (Fig. 1) that led to the diagnosis of sarcoidosis with probable cardiac involvement.

Echocardiography showed a mildly dilated left ventricle and wall thickening of the interventricular septum with normal left ventricular (LV) wall motion [LV end-diastolic dimension (LVDd): 58.1 mm, LV end-systolic dimension (LVDs): 38.9 mm, end-diastolic thickness of interventricular septum (IVSd): 19.5 mm, end-diastolic thickness of LV posterior wall (LVPWd): 10.8 mm, LV ejection fraction (LVEF): 61%] (images not available due to having already been disposed).

At 36 years of age, the pacemaker was re-implanted because of an infection, after which he was followed up at our hospital. In 2003, at 39 years of age, he began to notice dyspnea on effort associated with gradually progressing LV dilatation with reduced LV systolic function demonstrated by echocardiography (LVDd: 76 mm, LVDs: 67 mm, IVSd: 8 mm, LVPWd: 10 mm, LVEF: 25%). In 2004, at 40 years of age, he was admitted to our hospital, and steroid therapy was initiated in addition to medical treatment for heart failure with a beta-blocker (carvedilol), an angiotensin II recep-

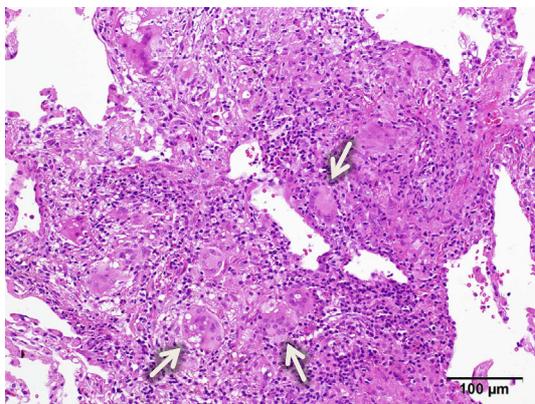
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tor blocker (losartan potassium) and an anti-aldosterone agent (spironolactone). Diuretics (azosemide and torasemide) were added later, and he was followed up at our outpatient department.

In 2013, at 49 years of age, he was readmitted to our hospital due to progressive heart failure symptoms with a severely deteriorated cardiac function. Echocardiography showed a markedly dilated left ventricle with a sharply reduced wall motion (LVDD: 90 mm, LVDs: 85 mm, IVSD: 8 mm, LVPWD: 11 mm, LVEF: 5%) (Fig. 2a and b). The plasma brain natriuretic peptide (BNP) level had increased to 2217.7 pg/mL. His pacemaker was upgraded to cardiac resynchronization therapy with a defibrillator (CRTD), which improved his heart failure (BNP: 666.7 pg/mL). How-



**Figure 1.** The biopsy of the lung using bronchoscopy. The presence of non-caseating epithelioid cell granulomas with multinucleated giant cells (arrows) is shown. Hematoxylin and Eosin staining, magnification:  $\times 200$

ever, an electrocardiogram showed a wide QRS complex even after CRTD implantation (Fig. 2c).

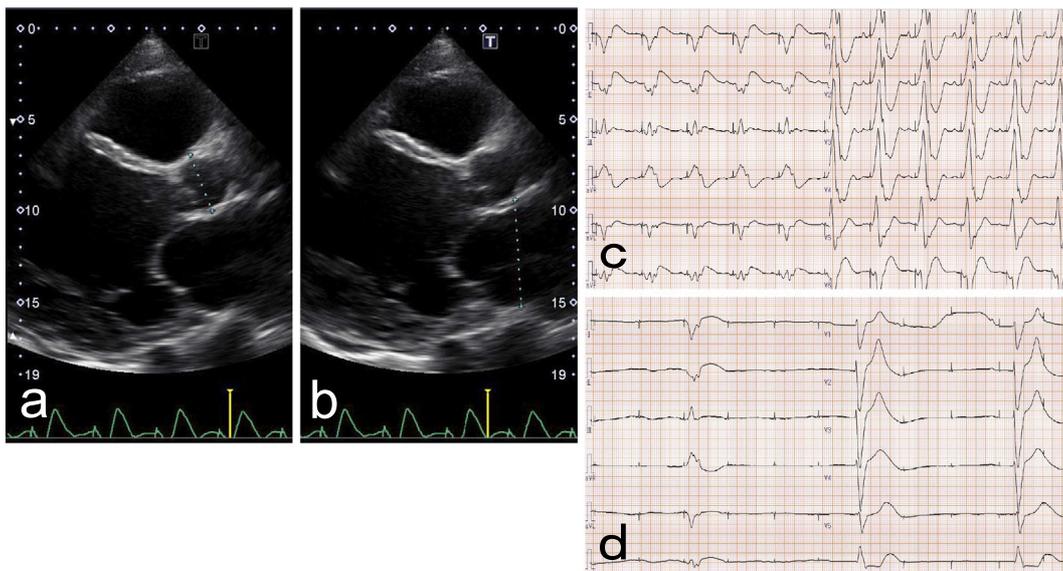
In 2017, at 53 years of age, he was admitted to our hospital by ambulance, because of depressed level of consciousness associated with hypotension. His systolic blood pressure was 50 mmHg, and an electrocardiogram showed sinus arrest and pacing failure with ventricular escape beats (Fig. 2d). Chest X-ray (Fig. 3a) and thoracic computed tomography (Fig. 3b) showed marked cardiomegaly with bilateral pleural effusion. However, despite intensive treatment, he died of multiple organ failure, and an autopsy was authorized only for the heart.

At the autopsy, the height was 183 cm and weight 74.8 kg. The heart was huge, with a weight of 1,500 g. The left ventricle was markedly dilated (Fig. 4a and b). Severe and diffuse interstitial fibrosis was observed, particularly at the lesion of the interventricular septum (Fig. 5). No sarcoid granuloma was found, but diffuse infiltration of macrophages was noted (Fig. 6, 7).

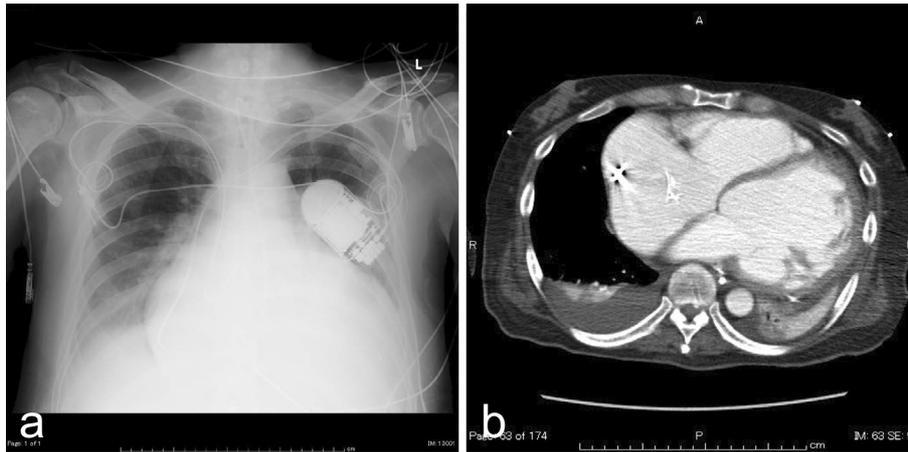
## Discussion

Notably, the heart in this case was extremely large, with a weight of 1,500 g. This is the heaviest heart ever recorded in our pathology department for the past 30 years. The LV wall, including the interventricular septum, retained its thickness, contrary to our expectations. Based on the echocardiographic findings, more thinning of the LV wall was expected.

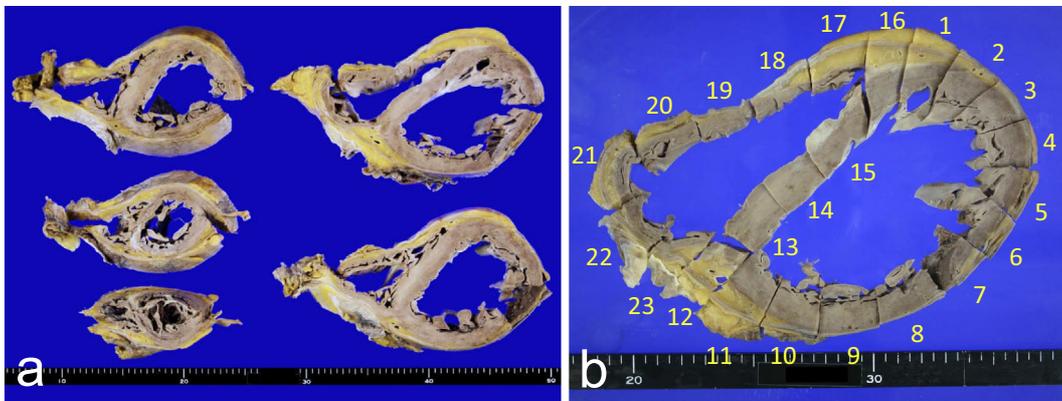
Even after careful observation of all sections, no sarcoid granuloma was found in this case. Considering the situation of disease onset in this case, the development of atrioven-



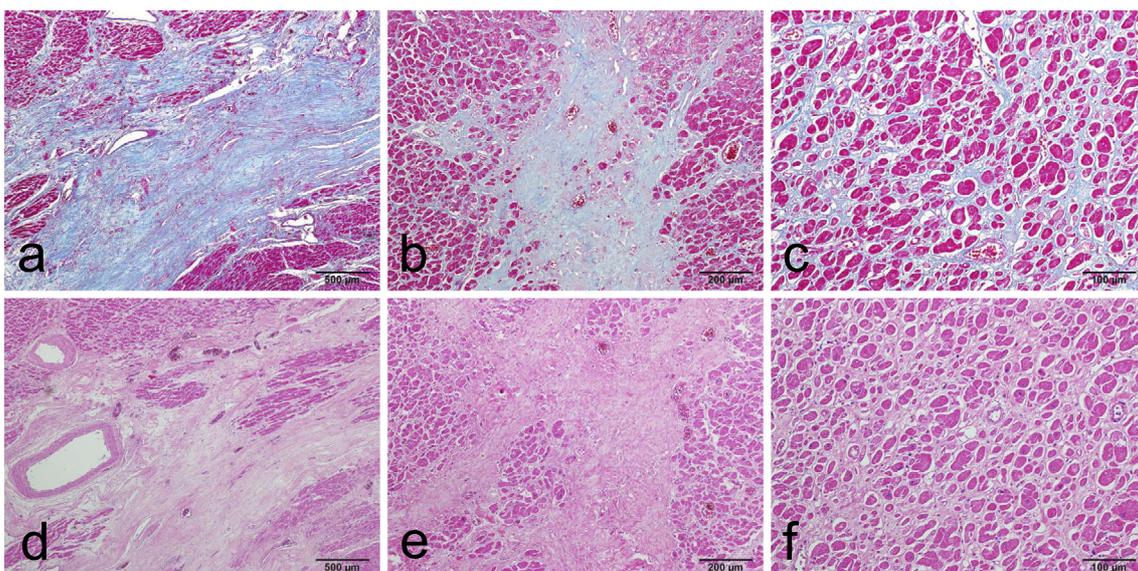
**Figure 2.** a, b: An echocardiogram on admission in 2013. Marked left ventricular dilatation with a severely reduced systolic function (left ventricular ejection fraction 5%) is shown (a: end-diastole, b: end-systole). c: An electrocardiogram in 2016. The wide QRS complex is remarkable. d: An electrocardiogram at the last admission in 2017. Sinus arrest and pacing failure with ventricular escape beats are noted.



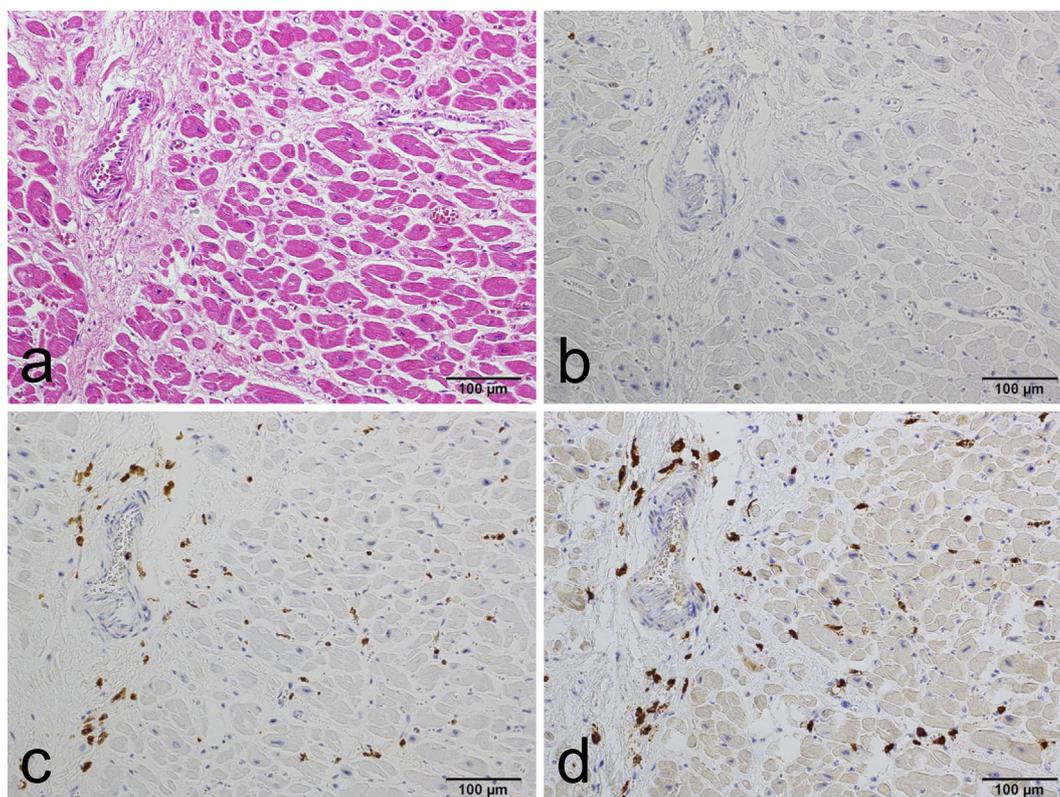
**Figure 3.** Chest X-ray (a) and thoracic CT (b) at the last admission in 2017. Marked cardiomegaly and bilateral pleural effusion are shown.



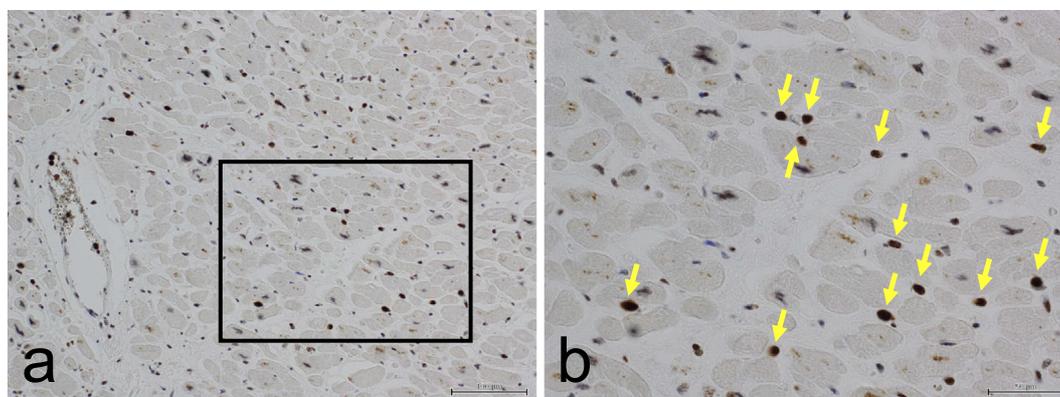
**Figure 4.** Macroscopic features of the autopsied heart. The heart is huge, weighing 1,500 g. The left ventricle is markedly dilated. The greyish white lesion in the ventricular wall is suggestive of fibrosis. a: Five slices of whole-area sections. b: Numbers of lesions for histological examinations



**Figure 5.** Histological findings of the interventricular septum (lesions indicated as number 14 and 15 in Fig. 4b) of the autopsied heart. Severe and diffuse interstitial fibrosis is present. Sarcoid granulomas are not found. a-c: Mallory azan staining, magnification: ×40 (a) ×100 (b) ×200 (c). d-f: Hematoxylin and Eosin staining, magnification: ×40 (d) ×100 (e) ×200 (f).



**Figure 6.** Immunohistochemical staining of the interventricular septum of the autopsied heart. Diffuse infiltration of mainly CD163-positive M2 macrophages is observed. a: Hematoxylin and Eosin staining, b: LCA, c: KP1, d: CD163, magnification:  $\times 200$ .



**Figure 7.** Immunohistochemical staining using anti-TGF $\beta$ 1 antibody of the interventricular septum of the autopsied heart (consecutive sections of the same block as Fig. 6). Infiltrating large mononuclear cells (probably monocytes/macrophages) are strongly positive for TGF $\beta$ 1 (arrows). a: Magnification:  $\times 200$ , b: Magnified image of the square area in (a). Magnification:  $\times 400$ .

tricular block and a reduced cardiac function, which was associated with BHL and a positive lung biopsy of sarcoid granulomas, the diagnosis of cardiac sarcoidosis is quite probable according to the diagnostic guidelines (1-3). Although there was no sarcoid granuloma in the myocardium in this case, it is one of the features of heart involvement in cases of sarcoidosis. Non-specific fibrosis is reportedly a histological variation in myocardial sarcoid lesions (4). These findings suggest that the active granulomas may have been replaced by fibrotic tissue and scar formation during

the healing process after myocardial injury which results in the loss of cardiomyocytes (5, 6), during steroid therapy.

The histological findings of focal patchy fibrosis (Fig. 5b and e) may reflect the scar of the sarcoid granulomas. However, it is somewhat interesting that not only severe replacement fibrosis but also diffuse endomyocardial fibrosis surrounding atrophied myocardial cells (Fig. 5c and f) were characteristic in this case. These findings may be histological features of the reactive phenomenon to long-term loading to the myocardium, leading to a severely deteriorated

rated cardiac function as the phenotype of dilated cardiomyopathy.

It is unusual that diffuse infiltration of macrophages was observed in this case. This was quite different from the histological characteristics of chronic myocarditis, which shows the focal infiltration of inflammatory cells (mainly lymphocytes). The immunohistochemical study revealed that most macrophages were M2 macrophages (Fig. 6). It appears as “acute myocarditis with the diffuse infiltration of M2 macrophages” that has not been reported so far to our knowledge. While the pathogenesis of this unique finding is unclear, the effects of certain drugs, such as catecholamines, used in the intensive treatment might be involved. In addition, immunohistochemical staining using the anti-transforming growth factor beta 1 (TGFβ1) antibody revealed that the infiltrating large mononuclear cells (probably monocytes/macrophages) were strongly positive for TGFβ1 (Fig. 7). Although this interesting finding is preliminary, it may suggest the involvement of TGFβ1-producing M2 macrophages in the development of severe cardiac fibrosis (7, 8) observed in this cardiac sarcoidosis case, and it may be partly related to the pathophysiology of the terminal stage of heart failure with ventricular remodeling (9).

From the clinical viewpoint of treatment, one important point may be the timing of starting steroid therapy. Based on the clinical record, it was obvious that the heart dilatation had progressed in the first five years from the onset, without steroid therapy. Corticosteroid therapy has been reported to improve the cardiac function and prognosis, and earlier intervention is considered to provide better therapeutic results (10-14). The clinical course would have been different had the steroid therapy been initiated earlier. However, we experienced a case of cardiac sarcoidosis showing spontaneous remission of inflammatory activity in the heart (15), and further investigations concerning the natural history of cardiac sarcoidosis will be necessary.

Another point to bear in mind is the indication of heart transplantation. Heart transplantation was not performed in the present case, mainly due to the patient's wishes but also due in part to our belief that a patient with cardiac sarcoidosis might not be an ideal candidate for such a procedure due to the potential for recurrence after the transplant (16).

### Limitations

The present patient was unable to undergo cardiac magnetic resonance imaging because he was using an implantable pacemaker. As he did not agree to undergo <sup>18</sup>F-FDG PET, we cannot describe the presence or absence of extra-cardiac lesions detected by imaging modalities as of 2013.

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

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### References

1. Terasaki F, Yoshinaga K. New guidelines for diagnosis of cardiac sarcoidosis in Japan. *Ann Nucl Cardiol* **3**: 42-45, 2017.
2. The Japanese Circulation Society (JCS). Guidelines for the diagnosis and treatment of cardiac sarcoidosis (JCS) (Chair: Fumio Terasaki) [Internet]. 2017 Feb 24 [cited 2019 Apr 1]; Available from: [http://www.j-circ.or.jp/guideline/pdf/JCS2016\\_terasaki\\_h.pdf](http://www.j-circ.or.jp/guideline/pdf/JCS2016_terasaki_h.pdf) (in Japanese)
3. Birnie DH, Sauer WH, Bogun F, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm* **11**: 1305-1323, 2014.
4. Matsui Y, Iwai K, Tachibana T, et al. Clinicopathological study on fatal myocardial sarcoidosis. *Ann NY Acad Sci* **278**: 455-469, 1976.
5. Schelbert EB. Myocardial scar and fibrosis: the ultimate mediator of outcomes? *Heart Fail Clin* **15**: 179-189, 2019.
6. Berkenboom G, Hulet F, Rimmelink M, Unger P. Severe myocardial fibrosis in a patient with cardiac sarcoidosis. *Acta Cardiol* **68**: 231-232, 2013.
7. Murray PJ, Wynn TA. Protective and pathogenic functions of macrophage subsets. *Nat Rev Immunol* **11**: 723-737, 2011.
8. Kong P, Christia P, Frangogiannis NG. The pathogenesis of cardiac fibrosis. *Cell Mol Life Sci* **71**: 549-574, 2014.
9. Nakayama T, Sugano Y, Yokokawa T, et al. Clinical impact of the presence of macrophages in endomyocardial biopsies of patients with dilated cardiomyopathy. *Eur J Heart Fail* **19**: 490-498, 2017.
10. Nagai T, Nagano N, Sugano Y, et al. Effect of corticosteroid therapy on long-term clinical outcome and left ventricular function in patients with cardiac sarcoidosis. *Circ J* **79**: 1593-1600, 2015.
11. Chiu CZ, Nakatani S, Zhang G, et al. Prevention of left ventricular remodeling by long-term corticosteroid therapy in patients with cardiac sarcoidosis. *Am J Cardiol* **95**: 143-146, 2005.
12. Kandolin R, Lehtonen J, Airaksinen J, et al. Cardiac sarcoidosis epidemiology, characteristics, and outcome over 25 years in a nationwide study. *Circulation* **131**: 624-632, 2015.
13. Yodogawa K, Seino Y, Ohara T, Takayama H, Katoh T, Mizuno K. Effect of corticosteroid therapy on ventricular arrhythmias in patients with cardiac sarcoidosis. *Ann Noninvasive Electrocardiol* **16**: 140-147, 2011.
14. Terasaki F, Ishizaka N. Deterioration of cardiac function during the progression of cardiac sarcoidosis: diagnosis and treatment. *Intern Med* **53**: 1595-1605, 2014.
15. Terasaki F, Fujita SI, Kanzaki Y, Hirose Y, Ishizaka N. Spontaneous reduction in abnormal myocardial uptake of fluorine-18 fluorodeoxyglucose in a patient with cardiac sarcoidosis. *Int Heart J* **59**: 647-651, 2018.
16. Yager JE, Hernandez AF, Steenbergen C, et al. Recurrence of cardiac sarcoidosis in a heart transplant recipient. *J Heart Lung Transplant* **24**: 1988-1990, 2005.

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