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CASE REPORT
Heart failure

Different reverse remodelling between left ventricle and right ventricle in fulminant heart failure due to giant cell myocarditis: a case report

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Background Giant cell myocarditis (GCM) is a rare cause of fulminant heart failure (HF). The most common presentation is progressive hemodynamic deterioration, and a few cases present with idiopathic complete atrioventricular block (cAVB). The prognosis of GCM is poor, and GCM patients usually die of HF and ventricular arrhythmia unless cardiac transplantation is performed. Few reports have described the effects of treatments such as immunosuppression and detailed reverse remodelling in GCM patients.

Case summary A 69-year-old female presented with cAVB. Transvenous pacemaker was implanted via the left subclavian vein. One and a half months later, she exhibited left ventricular dyssynchrony and lower left ventricular ejection fraction (LVEF), resulting in hospitalization for HF. She received cardiac resynchronization therapy; however, this had no apparently positive effects on her cardiac function. To investigate the cause of the lower LVEF, an endomyocardial biopsy was taken from the right ventricular septum. She was diagnosed with GCM and immediately received immunosuppression therapy with prednisolone and ciclosporin. This resulted in the functional recovery of the right ventricle; on the other hand, the left ventricle had still not recovered based on transthoracic echocardiography. Fortunately, she successfully recovered from severe HF without recurrence.

Discussion This is a case of fulminant HF due to GCM which initially presented as cAVB. Moreover, this case demonstrates the quite difference of the functional recovery between the left ventricle and the right ventricle with immunosuppression therapy.

Keywords Heart failure • Giant cell myocarditis • Endocardium biopsy • Case report

Learning points

- Giant cell myocarditis is a rare cause of fulminant heart failure (HF). However, it should still be considered even in patients with atypical clinical presentations.
- Endomyocardial biopsy should be performed at the early stage of HF with unknown cause.
- Although the left ventricular function did not recover after immunosuppression therapy, the recovery of the right ventricular function can improve the HF symptoms

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Introduction

Giant cell myocarditis (GCM) is a rare cause of fulminant heart failure (HF), and it is attributed to a T lymphocyte-mediated inflammation of the myocardium. Approximately 20% of cases associates with the systemic autoimmune diseases.[1,2] The most common presentation of GCM is progressive hemodynamic deterioration. In some cases, idiopathic complete atrioventricular block (cAVB) was present.[3] Clinical suspicion of GCM is a Class I indication for endomyocardial biopsy (EMB) to confirm the diagnosis.[4] The prognosis of GCM is poor, and patients usually die of HF and ventricular arrhythmia unless cardiac transplantation is performed.[1] The rate of death or cardiac transplantation was 89%, with a median survival of 5.5 months from the onset of symptoms to the time of death or transplantation.[1] Immunosuppression therapy is essential in the treatment of GCM, and more recent reports show that the 5-year survival of GCM treated with immunosuppression therapy was 52–72%.[2,5] Few reports have described in detail the reverse remodelling which occurs after immunosuppression therapy. We described a case showing the different myocardial remodelling between left ventricle and right ventricle in a GCM patient.

Timeline

Date	Event
Day 1	Transvenous pacemaker (PM) was implanted for complete atrioventricular block.
Day 8	She was discharged without any complications.
Day 43	She presented with exacerbation of shortness of breath and orthopnoea.
	She was re-hospitalized for worsening heart failure (HF).
	Transthoracic echocardiography demonstrated lower left ventricular ejection fraction and remarkable cardiac dyssynchrony.
Day 48	Intra-aortic balloon pump (IABP) was inserted because her HF was uncontrollable.
Day 50	Her treatment shifted from conventional PM to cardiac resynchronization therapy.
Day 65	IABP was extracted.
	Endomyocardial biopsy (EMB) was taken from her right ventricular septum. (①)
Day 71	She was prescribed with prednisolone 60 mg daily.
Day 85	She was prescribed with ciclosporin 100 mg daily.
Day 86	EMB was taken from right her ventricular septum. (②)
Day 124	EMB was taken from right her ventricular septum. (③)
Day 141	She was transferred to a rehabilitation hospital.

Case presentation

A 69-year-old female, who presented with cAVB (*Figure 1*, A-1), was referred to our hospital. Her past medical history was hypertension and dyslipidaemia, and she had been prescribed calcium channel blocker and statin. This time she had a history of syncope and exertional dyspnoea. Transthoracic echocardiography (TTE) revealed normal cardiac function [left ventricular ejection fraction (LVEF): 67.2%, *Video 1*] and no significant valvular heart disease. Dual-chamber pacemaker (PM) was implanted via the left subclavian vein (*Figure 1*, B-1). She was discharged on Day 8 without any complications. One and a half months later (on Day 43), she presented with exacerbation of shortness of breath and orthopnoea. TTE demonstrated akinesis in the anterior wall, cardiac dyssynchrony, and LVEF at 47.7% (*Videos 2 and 3* and Supplementary material online, *Video S1*). Chest radiography showed mild congestion (*Figure 1*, B-2). Laboratory tests showed increased brain natriuretic protein (BNP) at 3352.3 pg/mL (reference value 0–18.4 pg/mL) and myocardial deviation enzymes [creatinine kinase (CK): 639 U/L (reference value 42–135 U/L), CK-MB: 39 U/L (reference value 0–25 U/L), troponin I: 20.58 ng/mL (reference value 0–0.045 ng/mL)], and normal kidney function (estimated glomerular filtration rate: mL/min/1.73 m^2). Acute coronary syndrome was suspected, and emergent coronary angiography was performed. However, the coronaries had no significant stenosis, and she was diagnosed with worsening HF and was hospitalized. Her HF status did not improve after receiving drugs for HF, such as diuretics and dobutamine. Intra-aortic balloon pump was inserted on Day 48, and TTE demonstrated worsening LVEF. We considered the possibility of the negative effect of right ventricular (RV) pacing on cardiac function, hence, on Day 50, her PM was upgraded to cardiac resynchronization therapy (CRT). TTE showed partial resynchronization, however, her respiratory status worsened mainly because of the fatigue and weakness of respiratory muscles. On Day 52, she was intubated with mechanical ventilation support (*Figure 1*, B-3). Tracheostomy was performed on Day 70. On Day 65, EMB was taken from her RV septum. The specimens demonstrated several giant cells, no granulomas, and diffuse myocardial interstitial fibrosis (*Figure 2*). Laboratory test results revealed normal angiotensin-converting enzyme and lysozyme levels. Her laboratory markers ruled out some autoimmune disorders (systemic lupus erythematosus, polymyositis, dermatomyositis, Sjögren's syndrome, rheumatoid arthritis, vasculitis, autoimmune thyroid disorder, and myasthenia gravis). Whole-body computed tomography showed no sign of sarcoidosis, such as hilar lymphadenopathy. Finally, she was diagnosed with GCM. She was prescribed prednisolone (PSL) 60 mg daily on Day 71 and ciclosporin 100 mg daily on Day 85. Subsequently, her BNP decreased (*Figure 3*). EMB was taken from her RV septum twice more (on Days 86 and 124, three specimens/procedure), and the specimens demonstrated no giant cells and less apparent myocardial fibrosis (*Figure 4*). TTE showed no LVEF improvement (modified Simpson method) (from 37.2% at the beginning of PSL to 28.8% at discharge) (*Figure 3*). However, RV function significantly improved based on fractional area change (FAC) [from 17.5% at the beginning of PSL (Supplementary material online, *Video S2*) to 46.7% at discharge (*Table 1* and Supplementary material online, *Videos S3 and S4*)]. Intake of PSL was decreased to 30 mg daily upon discharge (tapered speed of 5 mg/week). She has not experienced any exacerbation of HF. Chest radiography showed no signs of lung congestion (*Figure 1*, B-4). She was transferred to a rehabilitation hospital on Day 141. The maximum

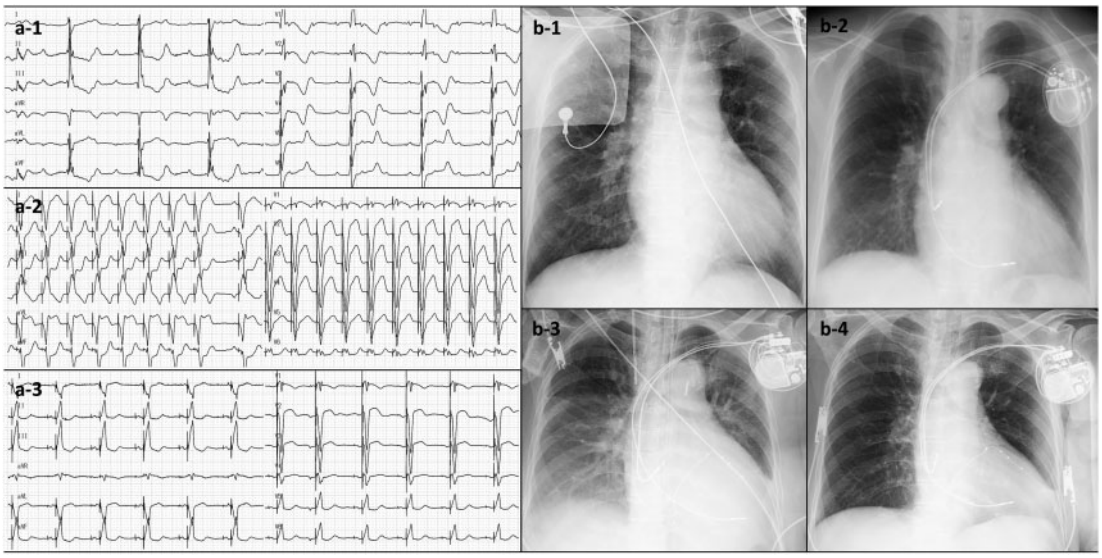


Figure 1 Serial electrocardiography and chest radiography. (*A*) Serial electrocardiography. (*A*-1) At the first visit to our hospital, (*A*-2) at the time of re-hospitalization for heart failure, and (*A*-3) at the time of discharge. (*B*) Serial chest radiography. (*B*-1) At the first visit to our hospital, (*B*-2) at the time of re-hospitalization for heart failure, (*B*-3) at the time of intubation, and (*B*-4) at discharge.

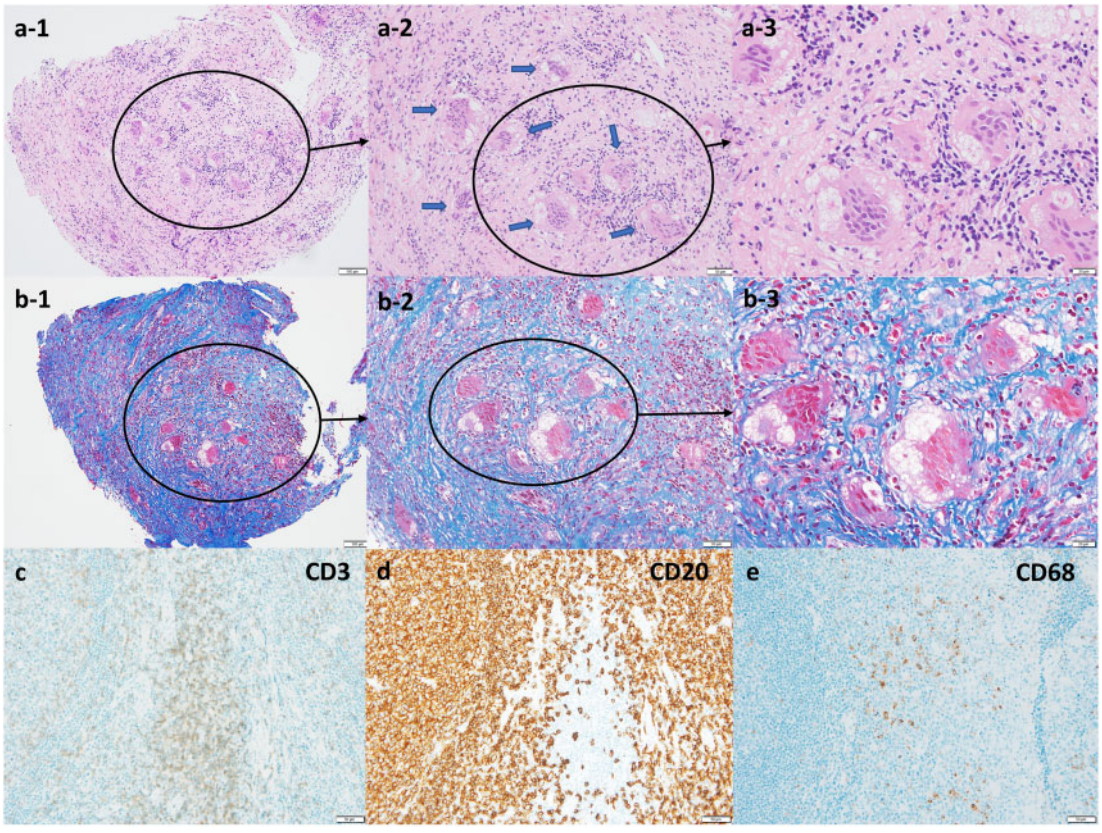


Figure 2 Endomyocardial biopsy from the right ventricular septum at diagnosis (on Day 65). (*A*) Haematoxylin–eosin stain, (*B*) Masson-Trichrome stain, (*C*) CD3 (T-cell), (*D*) CD20 (B-cell), and (*E*) CD68 (Macrophage). Blue arrows indicate giant cells. Figures showing myocyte injury caused by an inflammatory infiltrate variably composed of lymphocytes, macrophage, and multinuclear giant cells. Every bar located at the right below the area in every figure indicates 100 μm (*A*-1, *B*-1), 50 μm (*A*-2, *B*-2, *C*–*E*), and 20 μm (*A*-3, *B*-3).

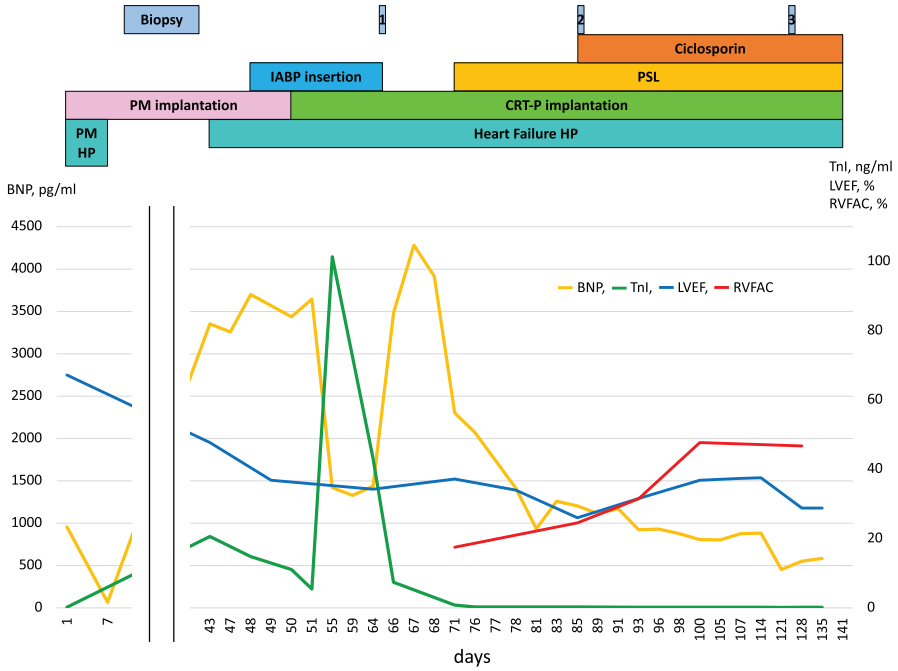


Figure 3 Timeline of this case showing brain natriuretic protein, troponin I, left ventricular ejection fraction, and right ventricular fractional area change from the onset of symptom to discharge. The information on immunosuppression medication, device, time of biopsy, and mechanical support was added to the figure. CRT, cardiac resynchronization therapy; HP, hospitalization; IABP, intra-aortic balloon pumping; LVEF, left ventricular ejection fraction; PM, pacemaker; PSL, prednisolone; RVFAC, right ventricular fractional area change.

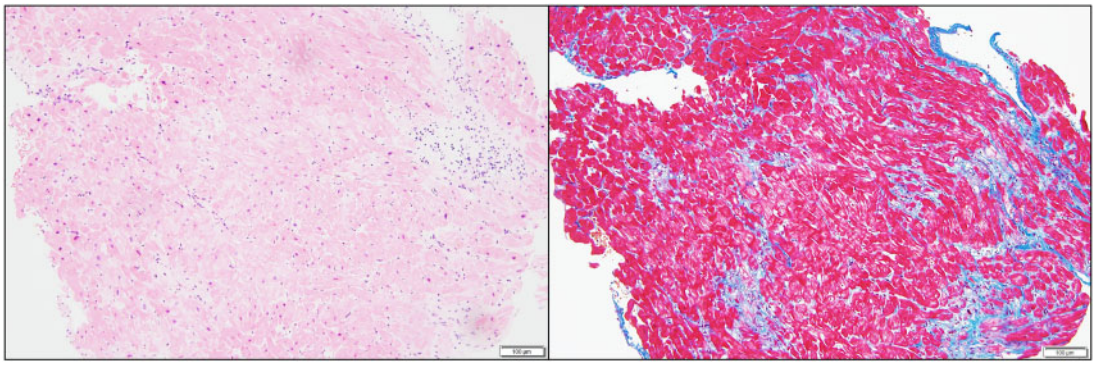


Figure 4 Endomyocardial biopsy from the right ventricular septum on Day 124. Histological figures showing no appearance of giant cells and less apparent myocardial fibrosis on Day 124 (left: haematoxylin–eosin stain, right: Masson-Trichrome stain). Every bar located at the right below the area in every figure indicates 100 μm.

values of CK, CK-MB, troponin I, and BNP during the HF hospitalization were 7444 IU/L (on Day 51), 228 IU/L (on Day 51), 101.33 ng/mL (on Day 56), and 4281.2 pg/mL (on Day 67), respectively. The HF drugs at discharge from our hospital were carvedilol 7.5 mg daily, perindopril 2 mg daily, furosemide 30 mg daily, spironolactone 25 mg daily, and tolvaptan 7.5 mg daily. She still continued rehabilitation at the rehabilitation hospital 3 months after the discharge from our hospital.

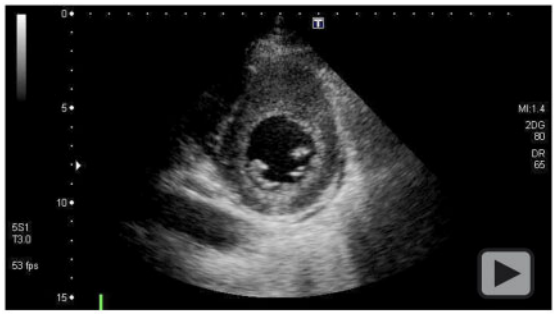
Discussion

The following features were observed in this case. First, an elderly female patient who initially presented with cAVB actually developed GCM. Second, after undergoing PM implantation, she had lower LVEF and cardiac dyssynchrony, and her PM was upgraded to CRT. However, the effect of CRT on HF status was relatively poor, therefore, EMB was taken, and she was diagnosed with GCM. Third, serial

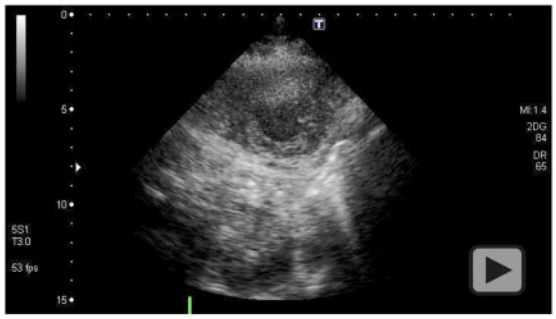
Table I Serial echocardiographic parameters

Date	LVEF (%)	LVDs (mm)	LVDd (mm)	LVESV (mL)	LVEDV (mL)	LVMI (g/m^2)	RWT	RVFAC (%)	TAPSE (mm	S′ (cm/s)
Day 1	67.2 (Teich)	27.6	43.8			175.0	0.65			20.2
Day 5	60.7 (Teich)	30.4	44.9			162.0	0.41			15.1
Day 43	47.7 (mod-Simpson)	34.9	46.6	47.5	90.9	178.8	0.57			
Day 49	36.8 (mod-Simpson)	38.2	48.3	51.8	81.9	173.4	0.52			10.8
Day 64	34.2 (mod-Simpson)	44.7	51.6	63.8	97.0	148.9	0.42			11.7
Day 71	37.2 (mod-Simpson)	45.8	52.8	62.2	99.1	115.1	0.33	17.5 S: 13.2 cm^2 D: 16.0 cm^2	16.1	10.9
Day 85	26.0 (mod-Simpson)	49.0	53.7	69.1	93.4	94.2	0.30	24.0 S: 13.6 cm^2 D: 17.9 cm^2	12.7	10.0
Day 93	31.6 (mod-Simpson)	47.8	54.1	80.7	118.0	104.3	0.29	31.5 S: 11.1 cm^2 D: 16.2 cm^2	16.8	12.3
Day 100	36.8 (mod-Simpson)	47.7	52.0	72.0	114.0	104.3	0.33	47.7 S: 5.81 cm^2 D: 11.1 cm^2	17.1	
Day 128	28.8 (mod-Simpson)	43.6	50.0	66.9	93.9	108.7	0.38	46.7 S: 6.98 cm^2 D: 11.9 cm^2	15.2	

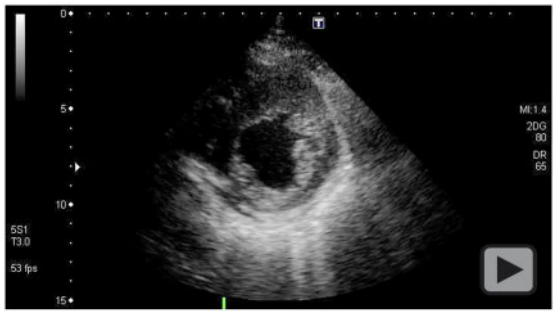
D, diastolic; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass index; Mod-Simpson, modified Simpson method; RVFAC, right ventricular fractional area change; RWT, relative wall thickness; S, systolic; TAPSE, tricuspid annular plane systolic excursion.



Video 1 Transthoracic echocardiography, long-axis view from parasternal at first visit (on Day 1).



Video 3 Transthoracic echocardiography, short-axis view from parasternal at second visit (on Day 43) (middle).



Video 2 Transthoracic echocardiography, short-axis view from parasternal at second visit (on Day 43) (basal).

echocardiographic data demonstrated the difference in the reverse remodelling between the left ventricle and the right ventricle after immunosuppression therapy.

Seventy-five percent of GCM patients presented with HF. Meanwhile, cAVB was observed in 5% of patients.[1] cAVB is a common disease among elderly people, and it is rarely associated with myocarditis. However, unexplained cAVB is one of the diagnostic symptoms of myocarditis.[6] Early EMB is indicated in patients who present with rapidly progressing HF and/or persistent cardiac troponin release.[2] EMB is the gold standard for diagnosing definitive myocarditis.[4] An EMB-guided approach is recommended in myocarditis presenting as acute HF with shock or high-grade heart block.[7]

The right ventricle plays a vital role in the morbidity and mortality of patients with several cardiac diseases.[8] The RV systolic function is a significant predictor of mortality in cardiovascular diseases, including HF.[9] In this case, although the LV function did not recover, the recovery of the RV function led to the improvement of HF status. Because of the unique anatomy of the right ventricle, its precise function evaluation is challenging.[10] A meta-analysis showed that FAC had a higher correlation with cardiac magnetic resonance (CMR) imaging-derived RV ejection fraction than with tricuspid annular plane systolic excursion.[11] Therefore, we evaluated the RV function using FAC. Serial echocardiographic data showed improvement of FAC, but not of LVEF. The follow-up biopsy specimens obtained from RV septum after immunosuppression therapy showed less interstitial fibrosis, indicating the recovery of the RV function in this patient (*Figure 4*). CMR is useful for confirming widespread but non-ischaemic necrosis in the acute phases of GCM.[12] In this case, we considered performing CMR, however, we did not push through because the patient was unstable and intubated, furthermore, she had undergone PM implantation and recently received CRT. We hypothesized that the difference in remodelling between the ventricles was due to the greater inflammation in the left ventricle than the right ventricle. CMR may have been able to elucidate more precise information on the myocardium. However, as seen in this case, patients with GCM are often unstable to undergo CMR imaging.[3]

Regarding the treatment, a small prospective study suggested that cyclosporine-based combined therapy reduced myocardial inflammation and improved clinical outcome.[1,13,14] Moreover, a case series involving 26 patients diagnosed with EMB described that 65% of the patients received azathioprine in addition to PSL and ciclosporin.[2] Choosing the optimal evidence-based immunosuppression regimen for the patients is challenging because there have only been some small case series and observational studies and no randomized clinical trials.[15] In this case, we prescribed only PSL and ciclosporin, not azathioprine. The LV function did not recover. However, PSL and ciclosporin treatment resulted in the recovery of the RV function and controlled HF symptoms. We were cautious about the side effects of multi-immunosuppression therapy.

Lead author biography

Hiroaki Yokoyama is working in Shonan Kamakura General Hospital from 2017.4. He was graduated from Nagoya University in 2013. He finished resident program (2013.4–2015.3) and fellowship in Internal Medicine (2015.4–2017.3) and Cardiology (2017.4–) in Japan. Membership: Japanese Circulation Society, Japanese Association of Cardiovascular Intervention and Therapeutics.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient's family in line with COPE guidance.

Conflict of interest: None declared.

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