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CASE REPORT
Other

High-sensitivity cardiac troponin serving as a useful marker for the early recognition of relapse of isolated cardiac sarcoidosis: a case report

Akira Tashiro *, Yasuaki Tanaka, Hiroyuki Hikita, and Atsushi Takahashi

Cardiovascular Centre, Yokosuka Kyosai Hospital, 1-16 Yonegahamadori, Yokosuka, Kanagawa 238-8558, Japan

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Background Isolated cardiac sarcoidosis is a relatively rare disease that is difficult to manage because of challenges in determining the progression and flare-up of cardiac lesions. Routine reduction of glucocorticoid doses may lead to treatment failure and disease relapse, which are associated with increased mortality.

Case summary Herein, we present the case of a 49-year-old woman with isolated cardiac sarcoidosis in whom high-sensitivity cardiac troponin served as a biomarker for tailoring immunosuppressive therapy. She presented with progressive dyspnoea on exertion for 2 months and had elevated levels of high-sensitivity cardiac troponin I (hs-cTnI) at presentation. A diagnosis of isolated cardiac sarcoidosis was made based on the finding of electrocardiography, echocardiography, cardiac magnetic resonance imaging, and 18F-fluorodeoxyglucose (FDG) positron emission tomography. After the introduction of glucocorticoids, the hs-cTnI concentration immediately decreased, followed by the disappearance of FDG uptake in the heart. However, 2 months after oral prednisolone was reduced to the maintenance dose, the hs-cTnI concentration began to increase gradually, and 2 months later, worsening heart failure, progression of impaired left ventricular function, and de novo accumulation of FDG in the heart were observed, confirming the relapse of cardiac sarcoidosis. Intensified glucocorticoid therapy resulted in another immediate decrease in hs-cTnI concentration and improved heart failure management.

Discussion This case highlights the potential of hs-cTnI to serve as a serum biomarker for monitoring disease activity and response to immunosuppressive therapy in patients with cardiac sarcoidosis. The hs-cTnI could be a highly sensitive and cost-effective biomarker reflecting the inflammatory status of cardiac sarcoidosis.

Keywords Isolated cardiac sarcoidosis • Disease relapse • High-sensitivity cardiac troponin • Disease activity marker • Case report

ESC Curriculum 6.5 Cardiomyopathy • 6.2 Heart failure with reduced ejection fraction

Learning points

- Since there are no established disease activity biomarkers for cardiac sarcoidosis, it is challenging to recognize treatment failure or disease relapse of cardiac sarcoidosis early.
- In this case, high-sensitivity cardiac troponin was able to detect the relapse of cardiac sarcoidosis, even before the recurrence of symptoms and *de novo* imaging changes.
- High-sensitivity cardiac troponin can be a potential biomarker for monitoring the inflammatory status of cardiac sarcoidosis, given its poor prognosis after treatment failure.

* Corresponding author. Tel: +81 46 822 2710, Email: pakir@hotmail.co.jp
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Introduction

Sarcoidosis is a multi-system granulomatous disease of unknown aetiology that is characterized by non-caseating granulomas in affected organs, commonly the lungs, skin, eyes, and heart.[1] There is a certain population of patients with cardiac sarcoidosis with no organ involvement other than the heart, referred to as isolated cardiac sarcoidosis, which is challenging to diagnose because of the limited sensitivity of endomyocardial biopsy.[2] The mainstay of treatment for sarcoidosis with cardiac involvement and isolated cardiac sarcoidosis is immunosuppressive therapy using glucocorticoids. However, since there is no established method for monitoring response to glucocorticoid therapy, glucocorticoid doses are usually tapered automatically, and this may lead to disease relapse and treatment failure. We report an interesting case of a patient with isolated cardiac sarcoidosis, in whom high-sensitivity cardiac troponin served as a sensitive biomarker of disease activity and treatment response.

Timeline

2 months before presentation	Progressive dyspnoea on exertion started
2 weeks before presentation	Faintness and palpitations on exertion appeared
At presentation	Referred to our cardiology department Electrocardiogram revealed a third-degree atrioventricular block with torsade de pointes Echocardiography revealed abnormal ventricular wall motion and basal thinning of the ventricular septum High-sensitivity cardiac troponin I (hs-cTnI) was elevated to 217 pg/mL Coronary angiography was unrevealing Left ventriculography revealed aneurysmal formation Temporary cardiac pacing and heart failure management were started
2 weeks after presentation	Cardiac magnetic resonance revealed multifocal and broad areas of transmural late gadolinium enhancement
3 weeks after presentation	^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) revealed notable FDG accumulation in the heart Diagnosis of isolated cardiac sarcoidosis was made
5 weeks after presentation	Cardiac resynchronization therapy defibrillator was implanted
6 weeks after presentation	Oral prednisolone was initiated at 30 mg/day, then gradually decreased by 5 mg/day at intervals of 4 weeks Hs-cTnI declined sharply after initiation of prednisolone therapy
14 weeks after presentation	FDG-PET confirmed vanished FDG accumulation in the heart
30 weeks after presentation	Oral prednisolone was reduced to 5 mg/day
38 weeks after presentation	Hs-cTnI started to increase gradually
50 weeks after presentation	Dyspnoea on exertion reappeared
54 weeks after presentation	FDG-PET revealed *de novo* FDG accumulation in the heart. Relapse of cardiac sarcoidosis was confirmed Oral prednisolone was increased to 30 mg/day and methotrexate was introduced Hs-cTnI declined promptly after intensification of immunosuppressive therapy

Case presentation

A 49-year-old woman was referred to our cardiology department with progressive dyspnoea on exertion. The patient's medical history was unremarkable. She was healthy until 2 months prior to her visit, when she developed a persistent cough and experienced faintness, palpitations, and chest discomfort when walking. She appeared uncomfortable and was diaphoretic and orthopnoeic with bradycardia and bilateral lower limb pitting oedema at presentation. No visual disturbances or skin lesions were observed. Notably, initial laboratory evaluation revealed elevated high-sensitivity cardiac troponin I (hs-cTnI) (217 pg/mL) and brain natriuretic peptide (BNP) concentrations (580.9 pg/mL). Chest radiography revealed pulmonary congestion with bilateral pleural effusion. An electrocardiogram (ECG) revealed a third-degree atrioventricular block with torsade de pointes (*Figure 1*). Transthoracic echocardiography (TTE) revealed notable akinesis and wall thinning of the left ventricular basal anteroseptal wall and an impaired left ventricular ejection fraction (LVEF) of 43% without hypertrophy (see Supplementary material online, Video S1A). We suspected acute coronary syndrome and performed emergent coronary angiography after temporary cardiac pacing, which revealed smooth, unobstructed coronary arteries. However, left ventriculography illustrated remarkable left ventricular aneurysm formation that was inconsistent with the coronary blood flow (see Supplementary material online, Video S2). Endomyocardial biopsy was not performed because of haemodynamic instability. Chest computed tomography ruled out mediastinal or hilar lymphadenopathy. Cardiac magnetic resonance (CMR) revealed multifocal and broad areas of transmural late gadolinium enhancement in the apical anterior, mid-septal, inferior, and lateral wall (*Figure 2*), while ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) revealed notable FDG uptake in the septal and inferior walls of the heart without extracardiac abnormal FDG accumulation (*Figures 3* and *5A*). Serologic tests for viral myocarditis, rheumatologic diseases, and other systemic diseases, including serum angiotensin-converting enzyme, lysozyme, soluble interleukin-2 receptor, and interferon-gamma release assay for tuberculosis, yielded negative findings. Based on the above findings, a

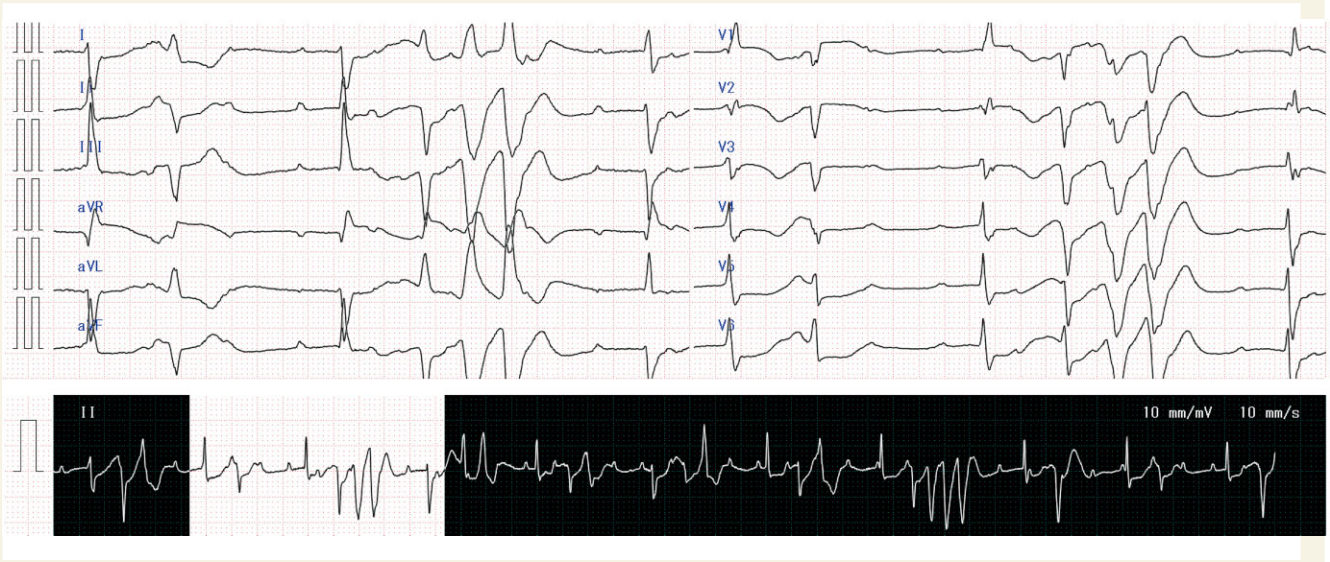


Figure 1 Electrocardiogram at the initial visit. The initial electrocardiography reveals a third-degree atrioventricular block with a junctional escape rhythm, QTc prolongation, and frequent non-sustained polymorphic ventricular tachycardia that were consistent with torsade de pointes.

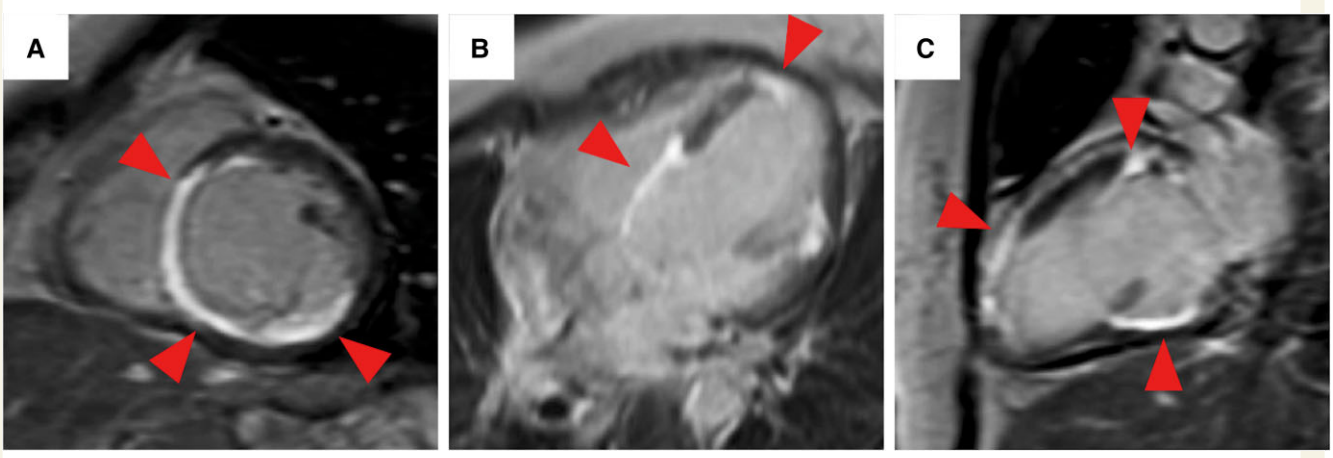


Figure 2 Cardiac magnetic resonance imaging. Late gadolinium enhancement images in the short-axis (*A*) and long-axis four-chamber (*B*) and two-chamber views (*C*) illustrate multifocal and extensive areas of transmural hyper-enhancement (arrowheads), which indicated non-ischaemic aetiologies.

diagnosis of isolated cardiac sarcoidosis was finally made on the 22nd day of admission, in accordance with the diagnostic criteria of isolated cardiac sarcoidosis in the updated Japanese Circulation Society guideline.[3] After heart failure management and cardiac resynchronization therapy with defibrillator were commenced, immunosuppressive therapy with oral prednisolone was initiated to reduce inflammation and to prevent further myocardial fibrosis and deterioration of cardiac function. Administration of prednisolone was initiated at 30 mg/day (0.5 mg/kg/day), gradually decreased by 5 mg/day at intervals of 4 weeks, and maintained at 5 mg/day. The hs-cTnI concentration declined sharply below the upper reference limit (<10 pg/mL) after the introduction of glucocorticoid therapy (*Figure 4*), followed by a subsequent decrease in BNP. ^{18}F-FDG PET/CT examinations performed 2 months after the initiation of prednisolone therapy indicated no cardiac FDG uptake (*Figure 5B*). However, despite the absence of symptoms and elevated BNP, the hs-cTnI concentration gradually increased to 254 pg/mL 2 months after reduction of the prednisolone dose to 5 mg/day. Two months later, dyspnoea on exertion worsened and elevated BNP levels were observed (*Figure 4*). Transthoracic echocardiography revealed a reduction in the LVEF to 25% (see Supplementary material online, Video S1B). The extent of active myocardial inflammation was re-evaluated using ^{18}F-FDG PET/CT, which revealed *de novo* FDG uptake at the apex of the heart (*Figure 5C*). A cardiac sarcoidosis relapse was

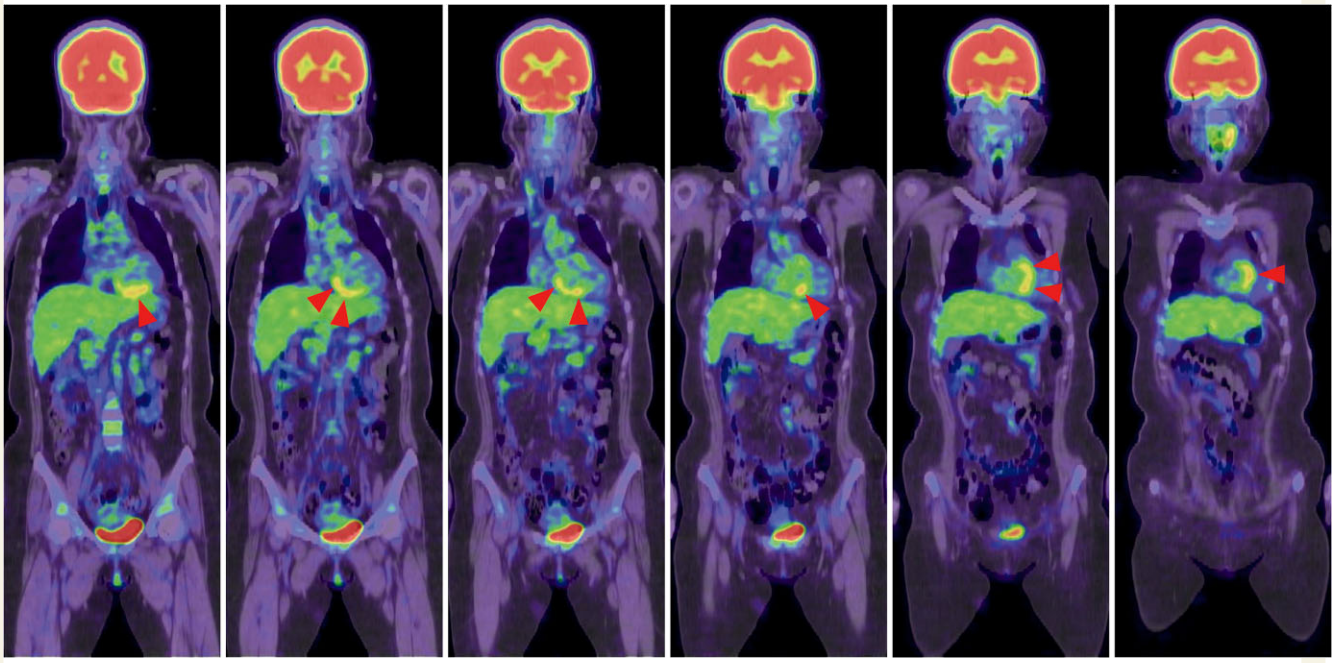


Figure 3 Whole-body ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography at baseline (coronal sections). Fluorodeoxyglucose positron emission tomography reveals increased ^{18}F-fluorodeoxyglucose uptake in the septal and inferior walls of the left ventricle (arrowheads). No extracardiac abnormal ^{18}F-fluorodeoxyglucose uptake was observed, consistent with isolated cardiac sarcoidosis.

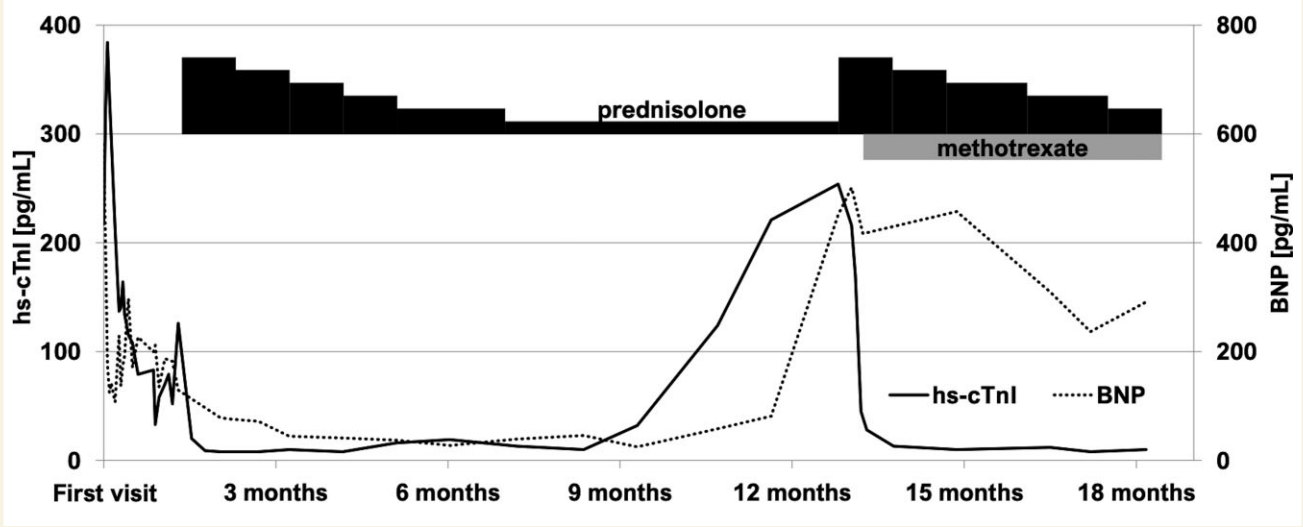


Figure 4 The association of immunosuppressive therapy with high-sensitivity cardiac troponin I and brain natriuretic peptide concentrations in cardiac sarcoidosis. The high-sensitivity cardiac troponin I concentration dropped sharply after the introduction of glucocorticoid therapy. However, the high-sensitivity cardiac troponin I concentration increased when prednisolone therapy was tapered to a maintenance dose, even before elevation of BNP levels and worsening of symptoms. The high-sensitivity cardiac troponin I concentration re-declined after the intensification of glucocorticoid therapy.

confirmed, and the prednisolone dose was increased to 30 mg/day followed by the addition of methotrexate at 6 mg/week, which resulted in a prompt reduction in the hs-cTnI concentration to <10 pg/mL and subsequent success of heart failure management, although the BNP levels were still elevated, revealing a discrepancy between hs-cTnI and BNP (*Figure 4*). The prednisolone dose was tapered by 5 mg/day at intervals of 4–6 weeks and maintained at 10 mg/day in combination with methotrexate at 6 mg/week. The patient's general

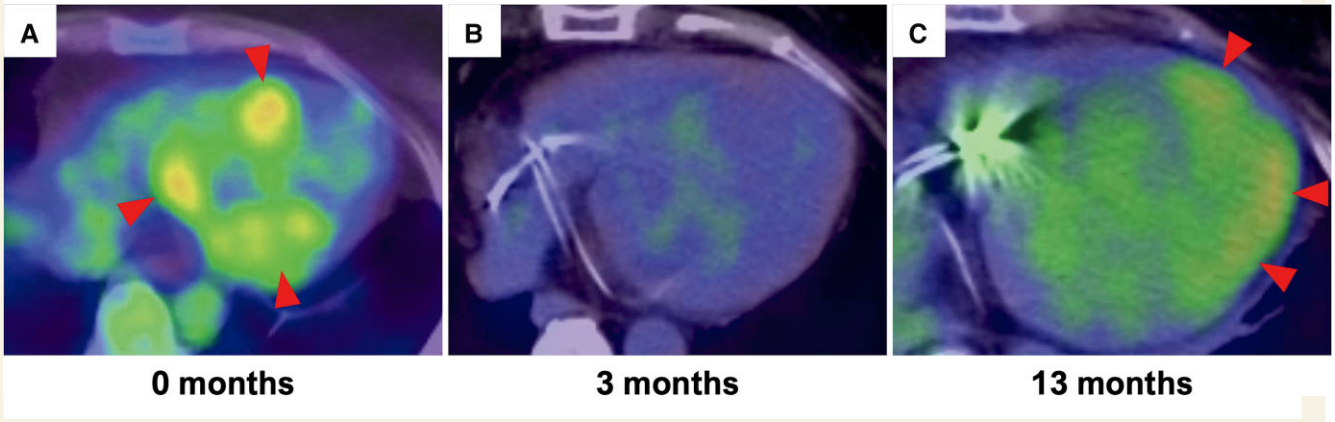


Figure 5 Serial ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography illustrates the changes in active inflammation of cardiac sarcoidosis. Fluorodeoxyglucose uptake was evident in the septal and inferior walls of the left ventricle (arrowheads) before the initiation of glucocorticoid therapy (*A*). ^{18}F-fluorodeoxyglucose uptake vanished after initiation of glucocorticoid therapy (*B*). However, *de novo* ^{18}F-fluorodeoxyglucose uptake was confirmed in the apex of the heart (arrowheads) after reduction of the prednisolone dose to 5 mg/day (*C*).

condition has remained stable, and the hs-cTnI concentration has been below the upper reference limit for over 3 years after the relapse.

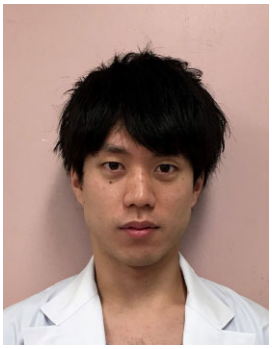
Discussion

We present an instructive case of isolated cardiac sarcoidosis in a 49-year-old woman in whom the hs-cTnI concentration was a useful biomarker for monitoring disease activity along with ^{18}F-FDG PET/CT. Generally, the diagnosis and management of cardiac sarcoidosis, especially isolated cardiac sarcoidosis, are challenging due to non-specific symptoms and the low diagnostic yield of ECG, TTE, cardiac scintigraphy, and endomyocardial biopsy. Further, no reliable serum biomarkers exist, including serum angiotensin-converting enzyme and lysozyme levels.[4,5] Cardiac magnetic resonance and ^{18}F-FDG PET/CT have high sensitivity and specificity in the diagnosis of cardiac sarcoidosis, but their limited availability and high costs prevent routine and repeated use.[6,7] Cardiac involvement is associated with a poor prognosis, necessitating early diagnosis and treatment.[8] Previously, elevated cardiac troponin was sometimes observed in cardiac sarcoidosis, with a decrease in these levels after the commencement of glucocorticoid therapy.[9,10] Another study suggested that patients with cardiac sarcoidosis depicting elevated cardiac troponin levels at presentation had a significantly lower LVEF and tended to exhibit more adverse cardiac events than those with normal cardiac troponin levels.[11] In this study, the hs-cTnI concentration decreased after glucocorticoid therapy was initiated and increased before a disease relapse that was confirmed by ^{18}F-FDG PET/CT, indicating that the levels of circulating cardiac troponin reflected the cardiac injury caused by cardiac sarcoidosis, and could serve as a sensitive biomarker of disease activity to optimize immunosuppressive therapy. Of note, the high-sensitivity cardiac troponin was able to detect the myocardial inflammation and predict the relapse of cardiac sarcoidosis as early as 2 months before the recurrence of symptoms in this case. This case suggests that in active-phase cardiac sarcoidosis, where large-scale myocardial damage occurs and cardiac troponins leak into the circulation above detection sensitivity, the value of cardiac troponins can be interpreted as a biomarker of its inflammatory activity, an indicator of treatment response, and a determinant of prognosis.

Conclusions

To our knowledge, this is the first case of isolated cardiac sarcoidosis that revealed the usefulness of high-sensitivity cardiac troponin for the early detection of disease relapse after tapering of glucocorticoid therapy. Considering the poor prognosis of cardiac sarcoidosis that is potentially caused by treatment failure or disease relapse, early recognition of cardiac injury using specific biomarkers is desirable.

Lead author biography



Dr Akira Tashiro graduated in Medicine at Tokyo Medical and Dental University (Japan) in 2015, and is currently working as an interventional cardiologist. His research interests include heart failure and cardiomyopathy as well as interventional cardiology and structural heart disease.

Supplementary material

Supplementary material is available at *European Heart Journal – Quality of Care and Clinical Outcomes* online.

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

Consent: The patient provided written informed consent for submission and publication of this case report and accompanying images in line with COPE guidance.

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References

1. Newman LS, Rose CS, Maier LA. Sarcoidosis. *N Engl J Med* 1997;**336**: 1224–1234.
2. Kandolin R, Lehtonen J, Graner M, Schildt J, Salmenkivi K, Kivistö SM, Kupari M. Diagnosing isolated cardiac sarcoidosis. *J Intern Med* 2011;**270**:461–468.
3. Terasaki F, Azuma A, Anzai T, Ishizaka N, Ishida Y, Isobe M, Nakatani S, Horii T, Yazaki Y, Yamaguchi E, Yamaguchi T, Ide T, Okamura H, Kato Y, Goya M, Sakakibara M, Soejima K, Nagai T, Nakamura H, Noda T, Hasegawa T, Morita H, Ohe T, Kihara Y, Saito Y, Sugiyama Y, Morimoto S-I, Yamashina A, Japanese Circulation Society Joint Working Group. JCS 2016 guideline on diagnosis and treatment of cardiac sarcoidosis—digest version. *Circ J* **2019**; 83:2329–2388.
4. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS, Judson Marc A., Kron Jordana, Mehta Davendra, Cosedis Nielsen Jens, Patel Amit R., Ohe Tohru, Raatikainen Pekka, Soejima Kyoko. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm* 2014;**11**:1305–1323.
5. Uemura A, Morimoto S-I, Hiramitsu S, Kato Y, Ito T, Hishida H. Histologic diagnostic rate of cardiac sarcoidosis: evaluation of endomyocardial biopsies. *Am Heart J* 1999; **138**:299–302.
6. Smedema JP, Snoep G, van Kroonenburgh MP, van Geuns RJ, Dassen WR, Gorgels AP, Crijns HJGM. Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis. *J Am Coll Cardiol* 2005;**45**: 1683–1690.
7. Youssef G, Leung E, Mylonas I, Nery P, Williams K, Wisenberg G, Gulenchyn KY, deKemp RA, DaSilva J, Birnie D, Wells GA, Beanlands RSB. The use of 18F-FDG PET in the diagnosis of cardiac sarcoidosis: a systematic review and metaanalysis including the Ontario experience. *J Nucl Med* 2012;**53**:241–248.
8. Yazaki Y, Isobe M, Hiroe M, Morimoto S, Hiramitsu S, Nakano T, Izumi Tohru, Sekiguchi M. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. *Am J Cardiol* 2001;**88**:1006–1010.
9. Baba Y, Kubo T, Kitaoka H, Okawa M, Yamanaka S, Kawada Y, Yamasaki N, Matsumura Y, Furuno T, Sugiura T, Doi YL. Usefulness of high-sensitive cardiac troponin T for evaluating the activity of cardiac sarcoidosis. *Int Heart J* 2012;**53**:287–292.
10. Tanada Y, Sato Y, Sawa T, Fujiwara H, Takatsu Y. Serial measurement of high-sensitivity cardiac troponin I and N-terminal proB-type natriuretic peptide in a patient presenting with cardiac sarcoidosis. *Intern Med* 2012;**51**:3379–3381.
11. Kandolin R, Lehtonen J, Airaksinen J, Vihinen T, Miettinen H, Kaikkonen K, Haataja P, Kerola T, Kupari M. Usefulness of cardiac troponins as markers of early treatment response in cardiac sarcoidosis. *Am J Cardiol* 2015;**116**:960–964.